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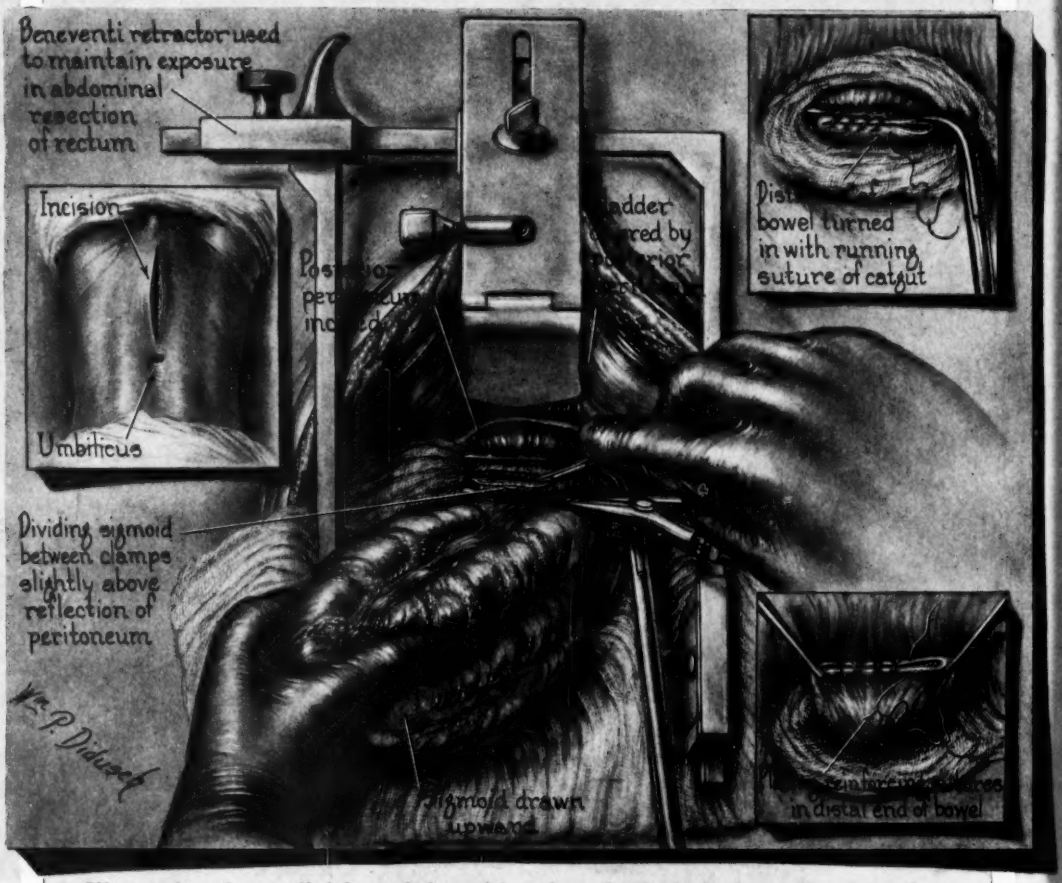
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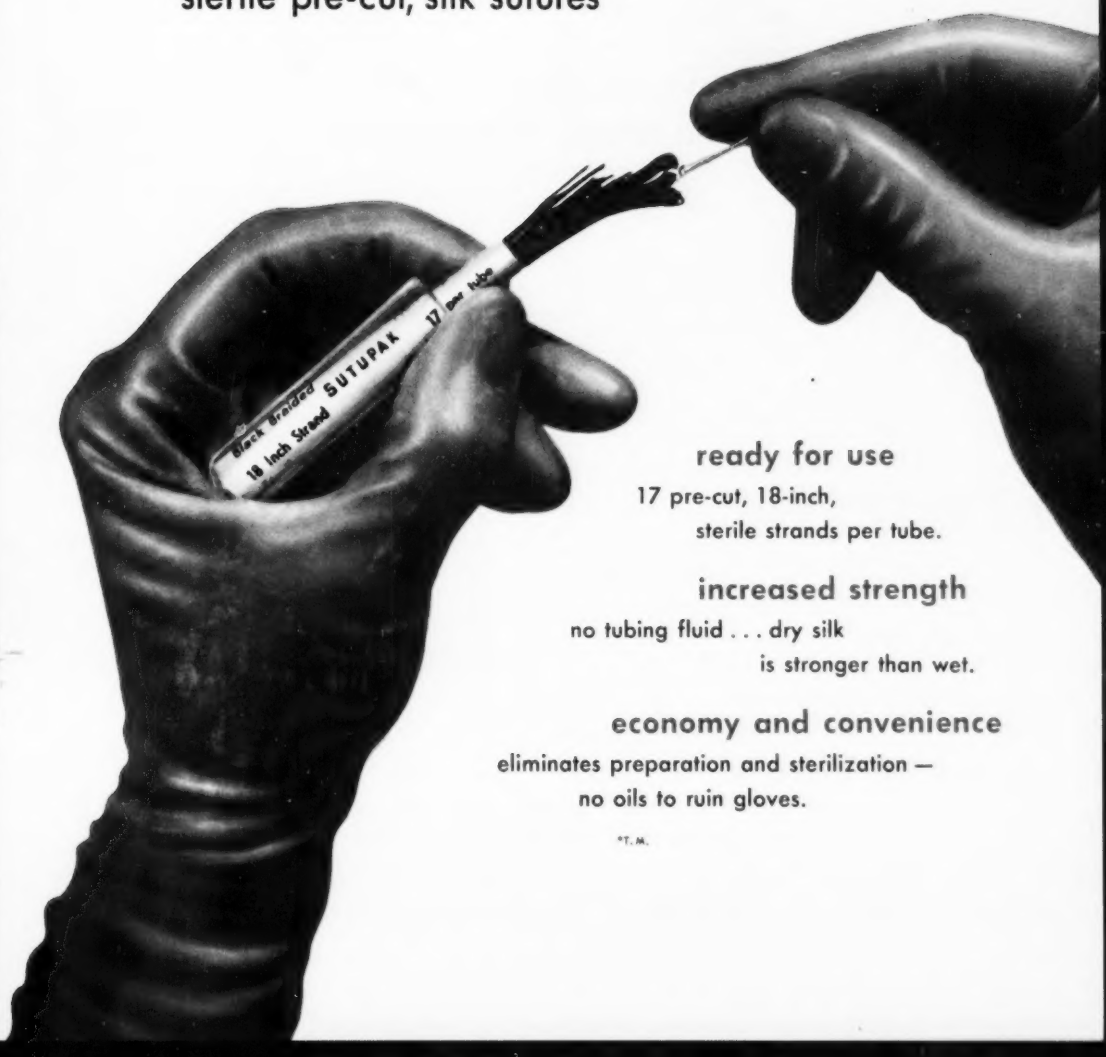

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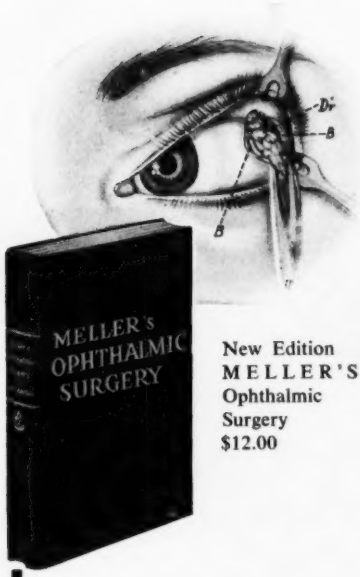

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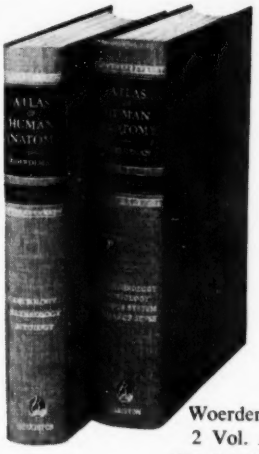

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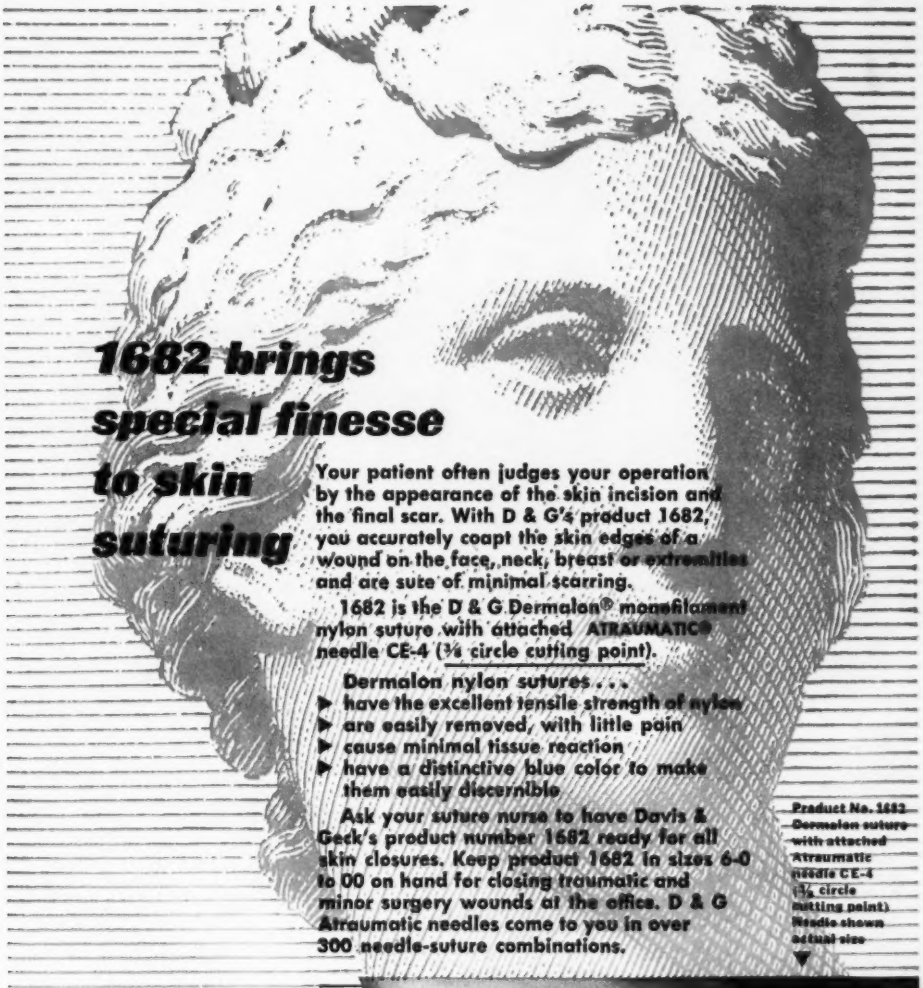

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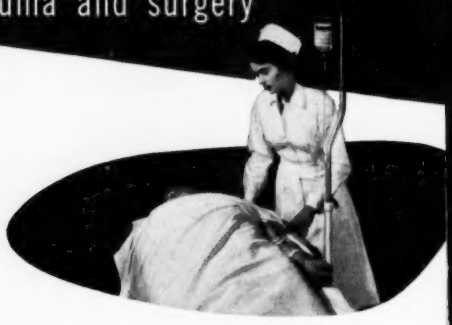

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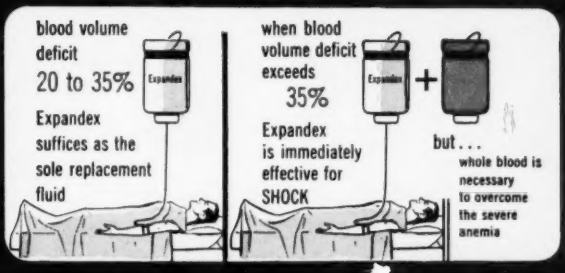
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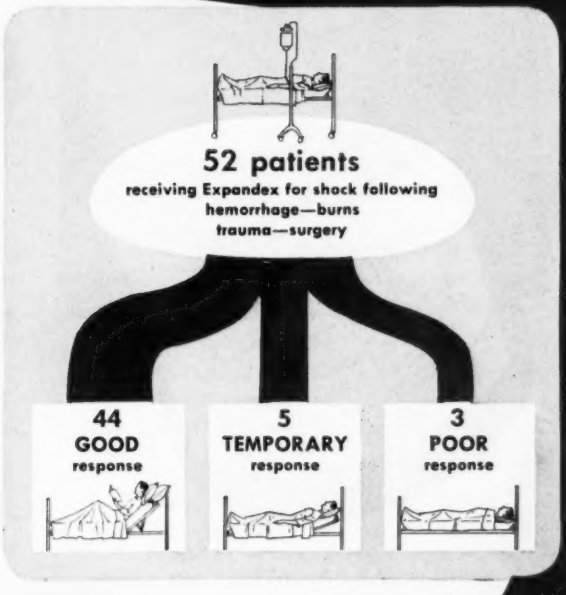

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Editorials

THE LONG-TERM PRESERVATION OF RED BLOOD CELLS

SINCE the advent of blood transfusion as an integral procedure in our therapeutic armamentarium, there has been a constant search for a method of preservation which would permit the prolonged storage of blood and its constituents. Application of the rapid freeze-dehydration principle solved the problem of preserving plasma, and stockpiling of this important fluid has been practiced since the early days of World War II.

Unfortunately, up to the present time, it has been impossible to preserve the cellular elements of the blood beyond a time period of three to four weeks. Consequently, because of the perishable nature of the red blood cell, the operation of our present day blood banks resembles more closely that of the fresh vegetable market than it does its monetary equivalent. This not only has been a definite handicap to maintaining a constant supply of blood during peacetime but has made the stockpiling of red cells for the continuing demands of national defense an utter impossibility. It is a very real tragedy that countless pints of precious red blood cells donated each year through our National Blood Program must be dumped down the sewers for lack of an adequate preserving process, following the preservation of the plasma fraction of whole blood. One investigator has calculated that this volume of red cells represents an annual loss greater than has been shed in battle by all American fighting men since Braddock's defeat.

Recently, two groups of investigators, working independently, have presented evidence that the long-term preservation of red blood cells may soon be possible on an economical and practical basis. Mollison and his associates in England [1] and Brown and Hardin [2] in this country have both been successful in preserving red blood cells in glycerin for over six months at subzero temperatures. As described by Brown and Hardin in this issue, the majority of such preserved red cells survive their normal life span when transfused at the end of the storage period, and this appears to be a significant observation.

Many problems must besolved before the glycerin preservation process can be considered practical. At present, the process described by the British workers and that described by the Duke University group result in losses of red cells varying

1. Mollison, P. L.; Sloviter, H. A., and Chaplin, H., Jr.: Survival of Transfused Red Cells Previously Stored for Long Periods in the Frozen State, Lancet **2**:501, 1952.

2. Brown, I. W., Jr., and Hardin, H. F.: Studies on the Recovery and in Vivo Survival of Human Red Cells After Storage up to 6¼ Months at Subzero Temperatures, A. M. A. Arch. Surg., this issue, p. 267.

from 30 to 50%. However, both groups have evidence that their present recovery and survival rates can be markedly improved by adopting new methods for removal of the intracellular glycerin prior to transfusion.

The trend of these studies may be far-reaching, as they indicate that means may be at hand for preserving red blood cells for at least one to three years and perhaps longer. It would appear that the only serious obstacle encountered by both groups of investigators has to do with the removal of the glycerin preservative before transfusion. It is hoped that this problem will soon be solved and that these important investigations will be encouraged and pursued as rapidly as possible. There is some indication that the British Medical Research Council, an operating as well as an advisory group, has already advocated an engineering project in this field. Academic competition in this or other specialized areas of science is wholesome but of minor import. The practical issue at stake stems from the real magnitude of our blood procurement program and the present and potential demands upon the full efficiency of this program.

Finally, it should be noted that Dr. Brown is a Markle Scholar. This work therefore seems to be a happy testimonial to the two-fold influence of a liberal university atmosphere and of a concept of long-term economic security upon the productive efforts of a talented scientist.

BARNES WOODHALL, M.D.

RECOVERY AND IN VIVO SURVIVAL OF HUMAN RED CELLS

Studies of Red Cells After Storage up to Six and One-Fourth Months at Subzero Temperatures

IVAN W. BROWN Jr., M.D.
AND
HILLIARD F. HARDIN, M.A.
DURHAM, N. C.

THE LONG-TERM preservation of blood plasma by freeze-drying has been successfully employed for a number of years, but attempts to prolong the preservation of red blood cells beyond 21 or 28 days have thus far proved unsuccessful. A method which would allow the long-term storage of red blood cells for transfusion purposes would be most desirable for peacetime medicine. The importance of such a method, permitting the stockpiling of red blood cells for the national defense for use in time of national emergency or disaster, is obvious.

Our interest in studying red blood cell preservation was originally stimulated by the work of Luyet,[1] who has presented evidence that intracellular crystallization of water is perhaps the most damaging of all subzero-temperature effects on living cells. On repeating his work,[2] we also succeeded in preventing the hemolysis of red cells caused by ordinary freezing. In addition, we succeeded in maintaining other tissues in a viable state for long periods by high velocity cooling and subzero storage in the vitreous (noncrystalline) state.[2] Our studies also confirmed Luyet's observations that preservation of viability at low temperatures is greatly facilitated if cells are first partially dehydrated and at least a portion of the intracellular water replaced by one of the lower polyhydric alcohols capable of moderate to rapid penetration of the cells. While these studies were in progress, Smith [3] presented further evidence for the beneficial effects of the polyhydric alcohols by reporting that whole blood in the presence of glycerin could be stored at —79 C. for periods up to three

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1. Luyet, B. J., in Panel V, Preservation of the Formed Elements and of the Proteins of the Blood, Washington, D. C., American Red Cross, 1949. Luyet, B. J., and Gehenio, P. M.. Life and Death at Low Temperatures, Normandy, Mo., Biodynamica, 1940.

2. Keeley, R. L. A.; Gomez, A. C., and Brown, I. W., Jr.: An Experimental Study of the Effects of Freezing, Partial Dehydration, and Ultra-Rapid Cooling on the Survival of Dog Skin Grafts, Plast. & Reconstruct. Surg. **9**:330, 1952.

3. Smith, A. U.: Prevention of Hæmolysis During Freezing and Thawing of Red Blood-Cells, Lancet **2**:910, 1950.

months without excessive hemolysis on thawing. Since then, Sloviter,[4] and Mollison and Sloviter [5] have extended Smith's observations. They showed that human red cells equilibrated with glycerin could be cooled to —70 C. for two hours, and in spite of considerable loss by hemolysis during processing, the remaining cells survived normally up to 60 days after transfusion.

More recently, and since the completion of our investigations described below, Mollison, Sloviter, and Chaplin [6] have reported post-transfusion survival studies of human red cells which have been stored at subzero temperatures up to 8½ months.

The following is a preliminary summary of our studies, still in progress, which have been conducted during the past two years on both quantitative recovery and in vivo survival of human red cells that were stored at subzero temperatures up to 6¼ months prior to transfusion. Further studies of processing methods and equipment along with in vivo survival studies of human red cells preserved and transfused after subzero storage up to one year are in progress, to be reported later.

STUDIES TO DETERMINE OPTIMAL CONDITIONS FOR SUBZERO PRESERVATION OF RED CELLS IN GLYCERIN

Immediately after the publication of Smith's report, in 1950, concerning the protective effect of glycerin on red cells stored at subzero temperatures,[3] we began a series of investigations to determine optimal conditions for the use of glycerin in preserving human red cells for transfusion purposes. The investigations included the following studies.

A. Red Cell Suspension Solutions for Subzero Storage.—From our earlier work [2] we had found that living cells retained their viability when exposed to high concentrations of the lower polyhydric alcohols. Smith, in her studies, had used equal parts of heparinized whole blood and 30% glycerin in either 0.85% sodium chloride or Ringer's solution. We found that by increasing the glycerin concentration, less red cell hemolysis resulted during the cooling and rewarming processes. In addition, it was apparent that when rapidly cooling red cells to —70 C. in low glycerin concentrations, the smaller the ratio of cells to suspending fluid, the less the hemolysis that resulted on thawing. Up to certain limits, the higher the glycerin concentration, the less important became the volume of the suspending fluid. We also found that the need for speed in cooling and rewarming became less important as higher concentrations of glycerin were used and that most human red cells, separated from their plasma, could be placed directly in 30 to 35% W/V glycerin at 5 C. and equilibrated at this temperature up to two hours without hemolysis. However, hemolysis occurred slowly and progressively increased if red cells were mixed directly with solutions of higher glycerin content.

To overcome this latter problem, we found that if red cells were first equilibrated with lower concentrations of glycerin (i. e., an equal volume of 30% W/V glycerin)

4. Sloviter, H. A.: Recovery of Human Red Blood-Cells After Freezing, Lancet **1**:823, 1951; In-Vivo Survival of Rabbit's Red Cells Recovered After Freezing, Lancet **1**:1350, 1951; Recovery of Human Red Cells after Prolonged Storage at —79 C., Nature, London **169**:1013, 1952.

5. Mollison, P. L., and Sloviter, H. A.: Successful Transfusion of Previously Frozen Human Red Cells, Lancet **2**:862, 1951.

6. Mollison, P. L.; Sloviter, H. A., and Chaplin, H., Jr.: Survival of Transfused Red Cells Previously Stored for Long Periods in the Frozen State, Lancet **2**:501, 1952.

the glycerin concentration could then be increased without red cell injury. By this means, we found that red cells could eventually be placed in concentrations of glycerin up to 56.25% W/V and equilibrated at 5 C. for one or two hours without hemolysis.

It was also noted that if red cells were stored in glycerin dissolved in isotonic sodium chloride solution, the red cell recovery on thawing became progressively less the longer the storage. This was particularly the case when higher subzero storage temperatures (—15 C.) were employed. It was found this hemolytic loss of cells could be largely prevented if the glycerin storage solution contained a salt, such as sodium lactate or sodium citrate, in isotonic concentration, whose anions were incapable of penetrating the red cells. While a number of nontoxic nonpenetrating salts were surveyed for this purpose, sodium lactate was chosen for our studies for reasons to be discussed later.

Smith [3] had studied whole blood to which glycerin solution was added. Inasmuch as it would be necessary to remove the glycerin before transfusing such red cells, to have employed her original procedure would have required the loss of valuable plasma. It was obvious that for any preservation method employing glycerin to be practicable, the plasma would have to be removed for freeze-drying or fractionation and the red cells preserved separately. When we repeated Smith's experiments, using red cells both with and without plasma, it was noted that the latter exerted a protective effect against hemolysis that became more apparent the longer the blood was stored at subzero temperatures. We have found that this protective effect can be obtained by the use of other easily obtainable and economical colloids capable of safe intravenous administration to human beings.

We have also studied other polyhydric alcohols and polyhydric alcohol derivatives for this purpose. However, as would be expected from their physical-chemical properties, only ethylene and propylene glycol gave results comparable to those of glycerin. In some respects propylene glycol seemed to present some advantages over glycerin, but the greater toxicity of propylene glycol and, especially, of ethylene glycol precluded their further investigation for this purpose.

In the past, both reduction and oxidation of the hemoglobin have been advocated for enhancing the preservation of red cells during storage. Experiments were performed in which reducing agents, such as ascorbic acid, were added to the storage solutions. Other glycerin storage experiments were conducted with completely oxygenated blood, but neither reduction nor oxygenation resulted in a noticeable improvement in red cell recovery from subzero storage.

Blood for subzero preservation experiments has been collected from blood donors in a number of different anticoagulant solutions. No significant difference in susceptibility to hemolysis during processing or in loss during thawing could be found among bloods collected in heparin, A. C. D.[7] (anticoagulant acid citrate dextrose) solution,[2] disodium ethylenediamine tetra-acetate ("equestrene"), or across a sulfonated polystyrene ("dowex 50") exchange resin in plastic containers. It was noted, however, that blood drawn into A. C. D. solution [7] withstood the glycerin-preserving process less well if allowed to stand at 5 C. in the original A. C. D.

7. A. C. D. solution contains disodium hydrogen citrate, 2.5 gm.; dextrose (anhydrous), 3.0 gm., and water, up to 100 cc.

solution for more than a few days. The effects of preliminary storage at 5 C. on blood drawn into the other anticoagulants has not been studied.

B. Freezing Characteristics of Glycerin-Lactate Solutions.—There is a marked tendency for the more concentrated glycerin-lactate solutions to supercool (if allowed to cool slowly) with a portion of the water freezing out of solution on standing or after agitation of the container. With bloods stored in glycerin solutions at —15 C., this supercooling allows the red cells to sediment to the bottom of the

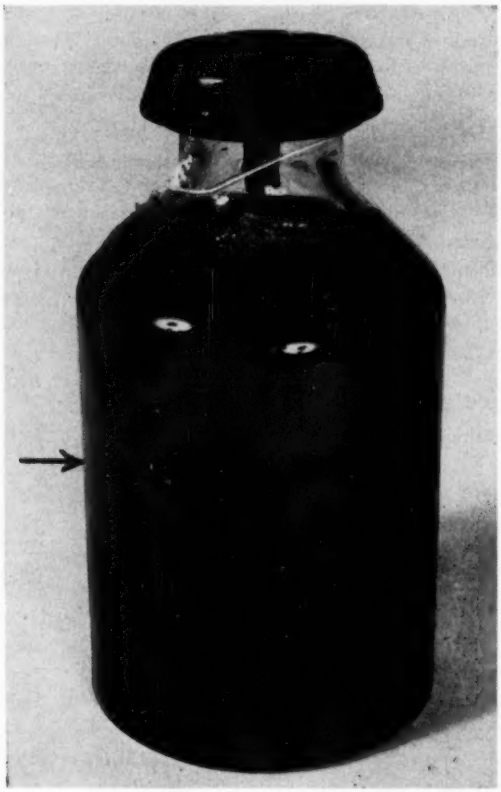

Fig. 1.—Bottle of red cells (from 500 cc. of whole blood) after storage for seven months at —15 C. in 50% W/V glycerin in 0.16 M sodium lactate. Photograph was taken immediately after removing bottle from —15 C. storage box. Note ice in supernatant fluid above level marked by arrow. Narrow zone of fluid below arrow and red cell layer are completely free of ice.

container before or while freezing of water takes place. When red cells are equilibrated with glycerin solutions of 50% W/V in 0.16 M sodium lactate and are stored at —15 C., the slowly forming ice crystals, because of their lower density, rise and coalesce in the solution above the cell layer (Fig. 1). This results in a partial phase separation of the water and glycerin, with a gradual increase in the glycerin concentration about the sedimented cells and a depression of the freezing point in this region. Undoubtedly, this explains the lack of ice in the red cell layer, the ability

to rewarm slowly without hemolysis, and perhaps in part, the better red cell recovery when higher glycerin concentrations are used for storage at —15 C.

As would be expected, the water in solutions of high glycerin content freezes out more slowly than in those of low glycerin concentration. If solutions of low glycerin content are cooled rapidly, the ice crystals tend to be smaller than when cooling is slow. In solutions of low glycerin concentration, more ice forms and remains uniformly distributed throughout the solutions. In contrast with solutions of high glycerin content, the rewarming of the former solutions is slower and requires more heat. Pure glycerin, because of the complexity of its liquid phase, the molecules being held together by a network of hydrogen bonds, has a rapidly increasing viscosity with decreasing temperatures. In addition, as the temperature is lowered, there is a reluctance for the hydrogen bonds to break, and this, with the increased viscosity, presents extremely unfavorable conditions for the glycerin molecules to orient themselves into the lattice of its crystalline form. Thus, glycerin is extremely difficult to crystallize at or below its freezing point (+17 C.); instead, it supercools at low temperatures, solidifying to the vitreous (glass-like) state at temperatures near —70 C.

We have found that concentrations of glycerin as low as 88% W/V will remain in the vitreous state for months at —70 C. Solutions of lower concentration may at first vitrify at this temperature, but over a period of weeks, water gradually freezes out until the whole solution becomes opaque with fine crystals of ice.

C. Blood Containers for Subzero Storage.—Numerous studies were carried out on various containers for processing and storing the red cells at subzero temperatures. Originally, it appeared that it would be necessary for such containers to meet the following criteria: (*a*) They should be economical and, perhaps, expendable. (*b*) They should be capable of heat sterilization. (*c*) They should be capable of as rapid heat transfer as possible. (*d*) They should be capable of withstanding severe thermal shock without breaking. (*e*) They should present a nontoxic and preferably nonwetting surface to the contained red cells.

Three such containers studied for red cell storage are shown in Figure 2. Plastic containers, because of their poor heat conductivity, were found impracticable when rapid cooling and rewarming was necessary, as in our early studies. Containers made of metal (Fig. 2 *B* and *C*) were found to be the most suitable for use when rapid freezing and rewarming was necessary (red cells in low glycerin concentrations stored at —70 C.). These latter containers were made of high heat conductivity metals. Their inner surfaces were either furnished with radial fins or in contact with a filler of metal strips; these devices permitted rapid cooling and rewarming without a large external surface area.

The conventional glass bottle and plastic containers have been found entirely suitable for storage at higher temperatures (—15 to —35 C.), particularly when higher concentrations of glycerin have been used.

D. Processes for Removal of Glycerin from Red Cells at the End of Storage and Before Transfusion.—It was evident that the most practicable way to remove the glycerin from the red cells before transfusion was by reversing the process by which it entered the cells. It was also evident that in so doing it would be necessary to keep the osmotic pressure relationships between the cells and their external environment in balance to prevent osmotic cellular injury and hemolysis. Consequently, a

number of nontoxic salts incapable of penetrating the red cell were studied. This scheme was based on the principle that the glycerin would diffuse out of the cells while an external osmotic pressure sufficient to prevent hemolysis was maintained by the wash solution of nonpenetrating ions.

A large number of sugars were tested for this purpose, but all were found to give too low osmotic pressures in practicable working concentrations. Some sugars

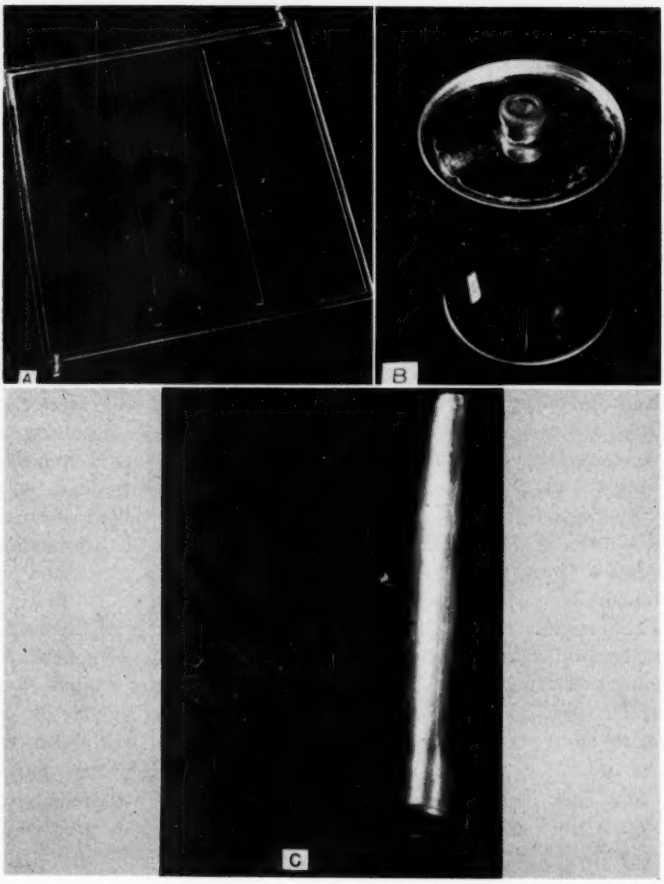

Fig. 2.—Three types of red blood cell storage containers which have been studied: *A*, thin-walled flat plastic container with large surface area for better heat transfer. *B*, metal can container used for blood stored at —70 C. These cans are loosely stuffed with coiled strips of polished aluminum. Before sterilization, strips and all internal surfaces of can were coated with heat-fixed silicone resin. *C*, tubular metal container with heavy internal fins (see cross section in left of photograph) for rapid heat transfer.

slowly penetrated the cells, causing their internal osmotic pressures to remain above that of plasma even after the glycerin was removed. Of the sugars tested, lactose was found the most suitable. A number of nontoxic salts containing either penetrating or nonpenetrating anions were also tested. Although hypertonic

solutions of these salts were successful in preventing osmotic hemolysis of the glycerin-containing cells, the majority, in the concentrations necessary initially, caused such severe and sometimes irreversible "sludging" of the cells on centrifuging as to preclude their use. A comparative study of these salts showed that the latter effect was least with sodium lactate solutions of equivalent osmotic pressures. Thus, in the experiments reported here, the glycerin was removed from the stored red cells by direct dialysis against hypertonic sodium lactate solutions. It was found that the presence of some glycerin greatly inhibited the sludging of cells caused by the initial and most hypertonic salt solutions. Consequently, in these experiments, some glycerin was added to the first postwarming wash solution of hypertonic sodium lactate and occasionally to the second wash, depending on the concentration of glycerin employed for storage.

Once the intracellular glycerin was removed, we found that an isotonic sodium chloride solution containing 3 to 5% lactose was a satisfactory red cell-suspending solution for transfusion.

PRESERVATION PROCESSES AND TECHNIQUES

A number of preservation studies with human blood, based upon the studies described above, have been made. These studies have led to continual improvements in our preservation processes and techniques. Most of these improved methods are still under study and have not yet been completely evaluated. However, the following studies made according to two of our earlier methods already indicate the strong possibilities for practicable prolonged preservation of red cells for transfusion purposes. The results of these studies are, in general, in agreement with the results of similar studies conducted concurrently in England and recently reported by Mollison and his associates.[6]

Preservation Method A, Storage at —70 C.—Donations of blood, 550 cc., from healthy male Group O donors (usually blood Group O N) were collected in conventional blood-donor bottles containing either heparin or chilled (5 C.) A. C. D. solution.[7] After samples were taken for duplicate total red cell counts and hematocrit readings, two calibrated 250-cc. volumetric flasks were filled to their marks from each blood bottle under sterile conditions. The contents of each of the flasks were then emptied, with rinses of isotonic saline, into separate dry sterile blood bottles. After these bottles were centrifuged, the supernatant plasma-A. C. D. solution in each bottle was aspirated. This was replaced with 300 cc. of cold (5 C.) 30% W/V glycerin in 0.16 M sodium lactate; the contents of each bottle were thoroughly mixed and allowed to stand at 5 C. for one-half hour. At the end of this equilibration period, the bottles were again centrifuged and the hemoglobin-free supernatant glycerin-lactate solution aspirated. The packed red cells remaining in each bottle were next transferred quantitatively into separate, specially prepared metal cans (Fig. 2*B*) of approximately 700-cc. capacity by rinses of cold (5 C.) 50.0% W/V glycerin in 0.16 M sodium lactate. In all, 300 cc. of the latter glycerin-sodium lactate solution was added to each can in addition to the red cells from the original 250 cc. of blood-A. C. D. solution mixture. After its contents had been thoroughly mixed, each can was rotated in an alcohol-dry-ice bath (—72 C.) for five minutes. This was found to be more than sufficient time for complete solidification of the blood-glycerin mixture. The cans were then stored in a constant low temperature cabinet at —70 C., where they remained until rewarmed for use.

Three to four hours pretransfusion, the stored blood was removed from the —70 C. cabinet and rapidly rewarmed by rotating the can while it was submerged in a water bath at 39 C. Rewarming the blood to the fluid state usually required five minutes' rotation in the water bath. However, the temperature of the blood was not allowed to rise above 5 or 10 C. during the rewarming process. The rewarmed blood-glycerin-lactate mixtures were then transferred to dry

blood bottles. The can was rinsed with 20% glycerin in 0.50 M sodium lactate in order to minimize loss of red cells by their retention in the storage can. The blood bottles were next centrifuged and the supernatant glycerin-lactate solution removed. This was slowly replaced, with mixing, by 300 cc. of 12.5% W/V glycerin in 0.48 M sodium lactate and the mixture allowed to equilibrate for 10 to 15 minutes at room temperature. The equilibration-centrifugation process was repeated with 300 cc. quantities of the following solutions: 5% glycerin in 0.48 M sodium lactate; 0.48 M sodium lactate, and 0.32 M sodium lactate.

After removal of the final supernatant above, the packed cells were transferred with rinses of 5% lactose in 0.9% sodium chloride solution, into the original resterilized 250-cc. volumetric flasks, and the contents were brought to the mark with additional lactose-saline. After thorough mixing, samples were taken for final duplicate red cell counts, hematocrit readings, and osmotic fragility studies. A measured amount of each red cell suspension was then transfused. In these early experiments where extreme caution was exercised, particularly in transfusing bloods that had been stored for months, minimum volumes of the stored cells were purposely transfused. Usually, for these transfusions, recipients of small stature and weight were chosen because of their lower red cell volumes. While the added steps of measuring the blood into volumetric flasks, both initially and prior to transfusion, were unnecessary for the preservation process, this was included in these studies in order to measure as accurately as possible the loss of red cells during storage and processing prior to transfusion. Thus, in the studies reported, we have separately measured red cell loss during subzero storage and processing and abnormal red cell loss after transfusion.

Preservation Method B, Storage at —15 to —18 C.—Donations of blood, 550 cc., were withdrawn from healthy male donors as described under Storage Method A. After duplicate total red cell counts were obtained, 500 cc. of the well-mixed blood from each bottle was measured by filling calibrated 500-cc. volumetric flasks to the mark. The contents of each of the flasks was then emptied with rinses of isotonic saline into dry sterile blood bottles, the bottles centrifuged, and the supernatant plasma-A. C. D. solution removed. This was replaced by 300 cc. of 30% W/V glycerin in 0.16 M sodium lactate and the contents of the bottles well mixed and allowed to equilibrate at 5 C. for 30 minutes.

After this, the bottles were again centrifuged and the supernatant glycerin-lactate solution removed and replaced with 300 cc. of 50% W/V glycerin in 0.16 M sodium lactate. After thorough mixing, the bottles were immediately placed in a refrigerator maintained between —15 and —18 C. where they were kept without agitation until rewarmed for use.

Three to four hours pretransfusion, the bottles were removed from the refrigerator and without mixing allowed to rewarm to above 0 C. either by standing at room temperature (20 C.) or in another refrigerator at 5 C. The supernatant glycerin-lactate solution was aspirated from the sedimented red cells and slowly replaced, with constant mixing, by 350 cc. of 18% W/V glycerin in 0.66 M sodium lactate. After the mixture was allowed to stand 10 to 15 minutes at 20 C., the bottle was recentrifuged and the process repeated with 350 cc. quantities of the following solutions: 6.0% W/V glycerin in 0.5 M sodium lactate; 0.5 M sodium lactate; 0.35 M sodium lactate, and 0.24 M sodium lactate.

After the aspiration of the final wash solution of sodium lactate, the packed red cells were transferred to the original resterilized volumetric flask with rinses of 5% lactose in 0.9% sodium chloride and the volume brought to the 500-cc. mark with the same solution. After thorough mixing, a sample was removed just prior to transfusion for final duplicate red cell counts, hematocrit readings, and osmotic fragility tests.

Methods of in Vivo Survival Study.—Transfusion recipients of both sexes were selected from among patients with pulmonary tuberculosis who had previously undergone thoracic surgery for removal of their diseased lung tissue. Only those patients were selected as recipients who had stable hemoglobin and red cell levels and in whom it was felt the disease had been controlled by the surgical therapy. Most of the recipients were at bed rest in sanatorium care throughout the experimental period. The fate of the transfused red cells was followed by counts of inagglutinable N donor red cells in M recipients, or Group O donor cells in Group A recipients. Each recipient's total red cell count and base line inagglutinable cell count were

determined at least three or four times within three days before transfusion. Base-line inagglutinable cell counts of the recipients ranged from 2,000 to 12,000. All inagglutinable cell counts were performed with potent antisera produced in rabbits and according to the modifications of DeGowin.[8] Four hemocytometer spreads from four cell-antiserum mixture tubes, prepared by four separate pipette measurements of the recipient's blood, were averaged in determining each inagglutinable count. Duplicate total red cell counts were made at the time of each inagglutinable count from the same blood sample. Between 500 and 4,000 inagglutinable cells were enumerated in determining each inagglutinable count, depending on the concentration of inagglutinable cells in the sample. The counting of large numbers of cells was facilitated by employing a photographic technique for enumerating the cells.[9]

Most of the transfusions were administered within a period of one-half hour. Samples for post-transfusion inagglutinable counts were taken within 30 minutes post transfusion and from most patients every few days thereafter throughout the observation period. In most cases, the recipient's plasma hemochromogen [10] and serum bilirubin [11] levels were determined immediately pretransfusion and at 30 minutes, 12 hours, and 48 hours post transfusion. The urine of each recipient obtained one hour post transfusion was examined for hemoglobinuria. Osmotic fragility tests [12] were made on a few of the stored cell suspensions just prior to transfusion. All recipients were carefully observed for symptoms and clinical signs of untoward reactions during the first 48 hours following transfusion.

Graphic Plotting of Data.—Each recipient's total red cell volume was determined immediately pretransfusion by the radioisotope P^{32} method, modified after Nachman,[13] employing the recipient's own freshly tagged red cells. Special rubber-tipped hematocrit tubes were employed. These tubes allowed the packed red cells from 5 cc. aliquots of blood to be determined to the nearest 0.01 cc. and recovered quantitatively and separately from supernatant plasma or saline. Correction factors for entrapped plasma [14] determined for our centrifuging conditions by the I^{131} method of Leeson and Reeve [15] were applied to all hematocrit readings.

The total red cell volume of both the stored blood and the recipient's blood (immediately pretransfusion) were employed in determining the theoretical 100% value of red cell survival. The use of these values has the advantage of eliminating differences in red cell concentration between venous blood and the average concen-

8. DeGowin, E. L.; Sheets, R. F., and Hamilton, H. E.: Studies with Inagglutinable Erythrocyte Counts: I. A Method for Measurement of Net Gain or Deficit of Red Cells in the Human Subject, J. Clin. Invest. **29**:693, 1950.

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10. Flink, E. B., and Watson, C. J.: A Method for the Quantitative Determination of Hemoglobin and Related Heme Pigments in Feces, Urine, and Blood Plasma, J. Biol. Chem. **146**:171, 1942.

11. Ducco, H., and Watson, C. J.: The Quantitative Determination of the Serum Bilirubin with Special Reference to the Prompt-Reacting and the Chloroform-Soluble Types, J. Lab. & Clin. Med. **30**:293, 1945.

12. Parpart, A. K., and others: The Osmotic Resistance (Fragility) of Human Red Cells, J. Clin. Invest. **26**:636, 1947.

13. Nachman, H. M.; James, G. W., III; Moore, J. W., and Evans, E. I.: A Comparative Study of Red Cell Volumes in Human Subjects with Radioactive Phosphorus Tagged Red Cells and T-1824 Dye, J. Clin. Invest. **29**:258, 1950.

14. A separate correction factor was determined for entrapped saline in the hematocrit of the washed tagged cell suspension injected for measuring the recipient's red cell volume.

15. Leeson, D., and Reeve, E. B.: The Plasma in the Packed Cell Column of the Haematocrit, J. Physiol. **115**:129, 1951.

tration for total body blood. In these studies, differences in mean corpuscular volume between donor and recipient blood were found to be negligible and have therefore been ignored.

Knowing the volume of donor cells transfused (X_v) and the recipient's pretransfusion red cell volume (Y_v), the ratio $\frac{X_v}{X_v + Y_v}$ is then equal to the unagglutinated fraction of the total red cell count that would be expected if all the cells transfused survived to the time of the first count.

All post-transfusion inagglutinable counts have been plotted in terms of the fraction of unagglutinated cells of the total red cell count (obtained on the same blood sample) expressed as percent of the expected ratio $\frac{X_v}{X_v + Y_v}$ described above. These calculations may be illustrated algebraically as follows:

Let

X_v = total volume of stored red cells transfused, in cubic centimeters
Y_v = recipient's pretransfusion total red cell volume, in cubic centimeters
X_{c1} = inagglutinable count/mm.^{3} at time t_1
Y_{c1} = total red cell count/mm.^{3} at time t_1 (from same sample as inagglutinable count t_1)

$$\frac{X_v}{X_v + Y_v} = R_o$$

where R_o is the fraction of stored cells that would be expected immediately post transfusion ($t = 0$) if all the stored cells survived the transfusion.
Then if the ratio R_o is used as the 100% value at $t = 0$, all subsequent counts are determined in percent survival as

$$\frac{X_{c1}}{Y_{c1}\ R_o} \times 100 = \text{percent survival at time } t_1$$

While the assumption is made that the recipient's red cell volume is stable throughout the observation period, plotting the data in this way corrects for the invariable fluctuations in whole blood volume.

RESULTS AND COMMENT

Data from eight transfusion experiments employing red cells which had been stored at subzero temperatures are given in the Table. It should be noted that for those red cells preserved at —70 C. the poststorage recovery of intact cells averaged 94% and ranged from 82 to 98%. The recovery of intact red cells after storage at —15 C. was 79%. These recovery results are considerably higher and more within the practicable range than those recently reported by Mollison and co-workers.[6] They recovered after thawing "about 50%" of red cells stored at —70 C. for six months, and only "about 20%" of red cells stored for a similar period at —15 C. We attribute our greater recovery of red cells to the use of higher concentrations of glycerin and to the use of sodium lactate in our freezing mixtures. The British workers stored red cells in special glass vessels, and after thawing, the glycerin was removed by dialysis through cellophane[8] for 36 hours. Our method of removing glycerin, as previously described, depends upon maintaining a low glycerin or glycerin-free environment of sufficiently high osmotic pressure about the cells to prevent hemolysis, while the intracellular glycerin gradually diffuses from the cells

TABLE.—*Data from Eight Transfusion Experiments*

Red Blood Cells, Unit	Storage Temperature, C.	Days Stored	Red Blood Cells Stored/ Mm.^{3} ($\times 10^4$)	Red Blood Cells Recovered After Storage/ Mm.^{3} ($\times 10^4$)	% Recovered	Volume Red Blood Cells Transfused, X_V (Cc.)	Recipient Pretransfusion Red Blood Cell Volume, R_V (Cc.)	$\frac{X_V}{X_V + R_V}$ *	c_t † (Time of Count Post Transfusion)	Xc_t ‡ ($\times 10^8$)	Yc_t § ($\times 10^4$)	$\frac{100\ Xc_t}{Yc_t\ R_0}$ ‖	% Normal Survival Post Transfusion ¶	% Over-All Survival ‡
A	—70	14	562.0	525.0	93	149.1	1498.0	0.0905	96 hr.	334.0	520.0	71	56	66
B	—70	19	489.0	480.0	98	175.6	909.1	0.1616	72 hr.	530.0	462.0	71	70	69
C	—70	21	447.0	427.0	96	156.2	1190.5	0.1160	72 hr.	457.0	489.0	81	71	68
D	—70	77	408.0	395.0	97	167.8	1246.7	0.1186	96 hr.	565.0	491.0	97	93	90
E	—70	141	458.0	449.0	98	51.0	1205.0	0.0402	144 hr.	96.0	478.0	50	50	49
F	—70	186	562.0	464.0	82	30.0	1095.0	0.0341	8 days	94.0	530.0	52	57	48
G	—70	190	562.0	517.0	92	33.0	977.0	0.0325	72 hr.	86.0	500.0	53	50	46
Average					94								64	62
H	—15	50	340.0	269.0	79	51.4	1503.0	0.0342	48 hr.	86.0	560.0	45	47	37

* For explanation of this ratio see text.

† c_t refers to the time post transfusion a count is taken.

‡ Xc_t = the corrected inagglutinable count/mm.^{3} at time c_t.

§ Yc_t = the recipient's total red cell count/mm.^{3} at time c_t determined from the same sample as Xc_t.

‖ $\frac{100\ Xc_t}{Yc_t\ R_0}$ = per cent survival of transfused cells at time c_t (for derivation see text).

¶ These values have been obtained from the survival curves (Figs. 4 and 5) by extrapolating the line of regression for the linear portion of the curves back to zero time.

‡ Over-all survival, as used here, takes into account the cells lost in storage and processing in addition to any initial abnormal loss post transfusion.

to satisfy a new equilibrium with the extracellular fluid. Recently, Lovelock [16] has advocated a similar scheme, suggesting the use of wash solutions of sodium citrate. Previously, we had discarded sodium citrate and certain other salts in favor of sodium lactate, because, in our experience, equivalent hypertonic solutions of the latter caused less coagulum-like aggregation of the cells on centrifuging. The use of hypertonic solutions of nonpenetrating salts has the advantage that it permits the

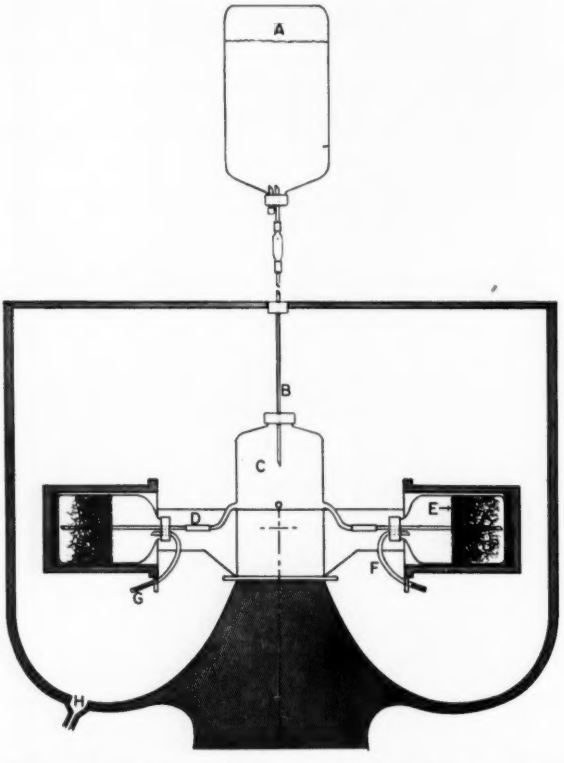

Fig. 3.—Diagrammatic sketch of experimental continuous-washing red cell centrifuge based on long traverse principle. Four bottles of red cells may be washed simultaneously. Sterile hypertonic sodium lactate from vessel (*A*) flows, at controlled rate, through long large bore needle (*B*) which pierces rubber diaphragm sealing hub distributing vessel (*C*) at its exact center. To insure seal and partially eliminate friction of rubber diaphragm rotating about stationary needle, top of sterilized rubber diaphragm is coated with heavy sterile silicone grease before needle is inserted. Metal hub distributing vessel (*C*), including its four delivery tubes (*D*), can be removed from centrifuge for cleaning and sterilizing. Once sodium lactate solution enters distributing vessel (*C*), it is forced out through delivery tubes (*D*) and through connecting large-bore needles that extend to bottoms of bottles. Glycerin-free sodium lactate solution entering bottom of packed cell layer sets up turbulence, causing cells to move forward as this less dense fluid mixes with glycerin solution. However, high gravitational force prevents cells from migrating beyond certain point (*E*). When bottle eventually fills, during continuous washing, overflow is carried off through tubes (*F*) which have one-way spring valves (*G*) preventing reflux or siphonage back into bottles. Overflow is caught by walls of centrifuge and flows out drain at (*H*).

16. Lovelock, J. E.: Resuspension in Plasma of Human Red Blood-Cells Frozen in Glycerol, Lancet **1**:1238, 1952.

glycerin to be removed from the cells more rapidly, in our experiments 3 to 4 hours. Blancher and Mayman [17] have suggested removing the intracellular glycerin by a logarithmic addition of large volumes of 1% saline to the thawed mixture of red cells and glycerin.

While our studies reported here were in progress, we began investigations of a continuous washing process for removal of intracellular glycerin, using a salt solution of gradually decreasing hypertonicity and centrifuging modified after the "long traverse method." [18] One type of apparatus studied is shown in Figure 3. While no in vivo survival studies have yet been made with red cells processed in such apparatus, it is now apparent that by gradually and continuously decreasing the

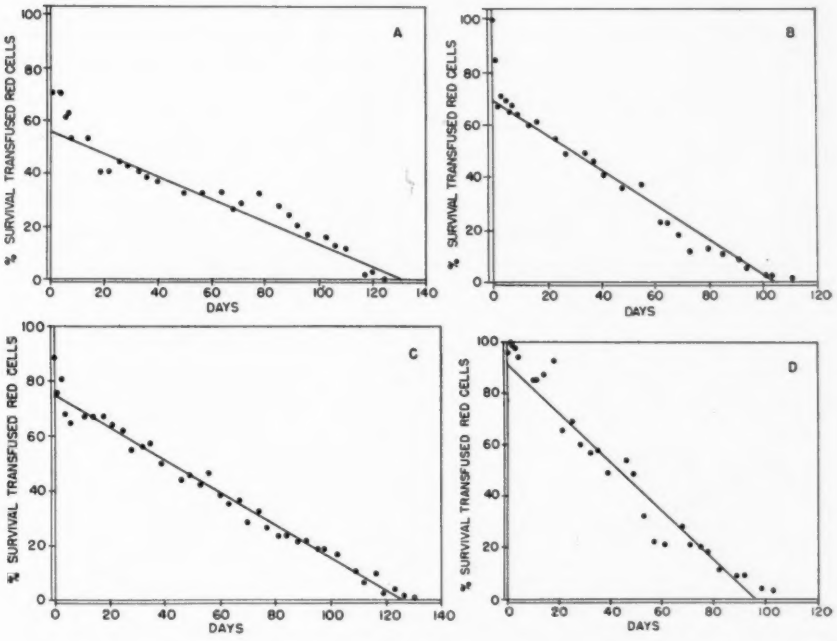

Fig. 4.—In vivo survival curves of four lots of red cells stored at —70 C. Curves (solid lines) above and those in Figure 5 have been fitted to data from linear portions by method of least squares. *A*, red cells stored 14 days before transfusion. Of red cells transfused, 56% survived normally. *B*, red cells stored 19 days before transfusion. Of cells, 70% showed normal in vivo survival. *C*, after 21 days of storage, 71% of the transfused red cells show normal survival curve. *D*, after 77 days of storage, approximately 93% of cells transfused show normal survival.

17. Blanchaer, M. C., and Mayman, C. I.: Glucose Utilization in Blood Cells Surviving Storage at —79 C., Canad. J. M. Sc. **30**:360, 1952.

18. Buckley, E. S., Jr.; Gibson, J. G., II; D'Hont, M. D., and Tinch, R. J.: Removal of Plasma from Erythrocytes Sedimented with Dextran by "Long Traverse Method" Centrifugation, Proceedings Conference on Separation of the Formed Elements, the Protein, Carbohydrate, Lipid, Steroid, Peptide and Other Components of Plasma, Section 10, July 11, 1950, University Laboratory of Physical Chemistry Related to Medicine and Public Health, Cambridge, Mass., Harvard University Press, 1950.

hypertonicity of the glycerin-free wash solution, rather than stepwise as described in these experiments, there is less osmotic injury to the cells, and the removal of intracellular glycerin is more complete.

The in vivo survival curves for the eight transfusions are shown in Figures 4 and 5. From these survival curves and from the data in Table 1, it will be noted that there was a marked variation between individual bloods as to red cell loss in the first few days post transfusion, ranging from 3 to 50%. Inasmuch as the circulation quickly rids itself of damaged red cells, this initial post-transfusion loss could have been due to the removal of cells which aged or died in storage, or were injured in processing, or both.

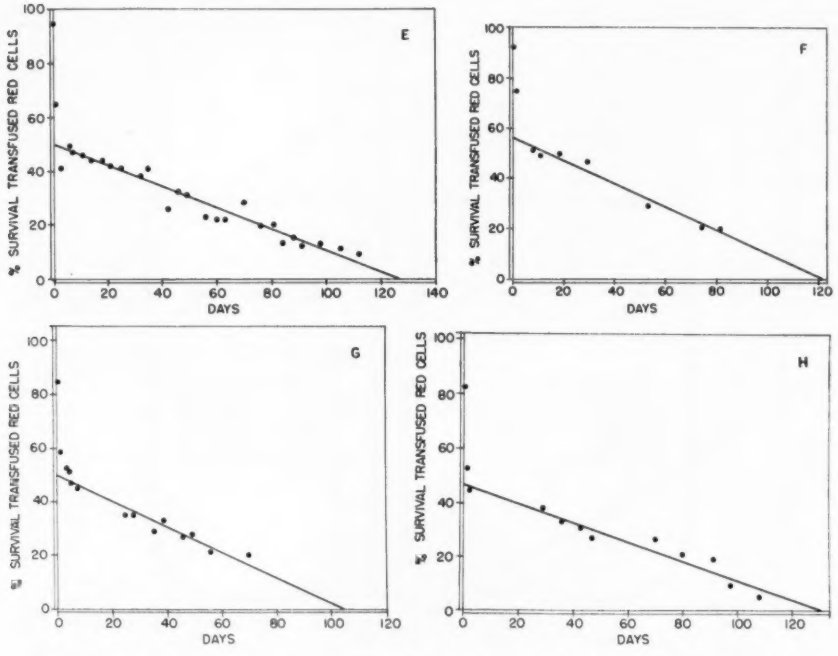

Fig. 5.—*E*, in vivo survival curve for red cells stored at —70 C. for 141 days. Of cells transfused, 50% show normal survival. *F*, survival curve for red cells stored at —70 C. for 186 days. Of transfused cells, 57% survived normally. *G*, survival curve for red cells stored at —70 C. for 190 days. Approximately 50% of cells transfused survived normally. *H*, survival curve for red cells stored at —15 C. for 50 days. Approximately 50% of red cells transfused showed normal survival.

Osmotic fragility curves determined just prior to transfusion on the cells stored at —15 C. for 50 days and the two lots stored at —70 C. for 186 and 190 days are shown in Figure 6. These curves show that between 10 and 20% of the red cells in each of these lots hemolyzed during the test (one-half hour at 37 C.) in the isotonic range of sodium chloride concentration. This would indicate that the contents of at least some of the cells were still hypertonic because of incomplete removal of glycerin. Undoubtedly, similar cells among those transfused hemolyzed shortly after entering the circulation of the recipients, probably accounting for at

least a portion of the initial post-transfusion red cell loss in these experiments. None of the recipients experienced any reactions to these transfusions of stored red cells.

A slight elevation of the post-transfusion serum hemochromagen level occurred in all the recipients in whom there was an immediate and significant loss of transfused cells, indicating that at least a part of those cells lost disappeared by intravascular hemolysis, rather than through sequestration by the reticuloendothelial system. One of the lots of cells transfused (blood D, Table 1; curve *D*, Fig. 4) was washed more slowly and with solutions of more gradual decrease in hypertonicity. These cells showed only a minimal loss (approximately 3%) immediately post transfusion.

Therefore there is evidence that a large part of the initial post-transfusion loss in these experiments was due to osmotic effects from the incomplete removal of intracellular glycerin, rather than from some storage lesion.

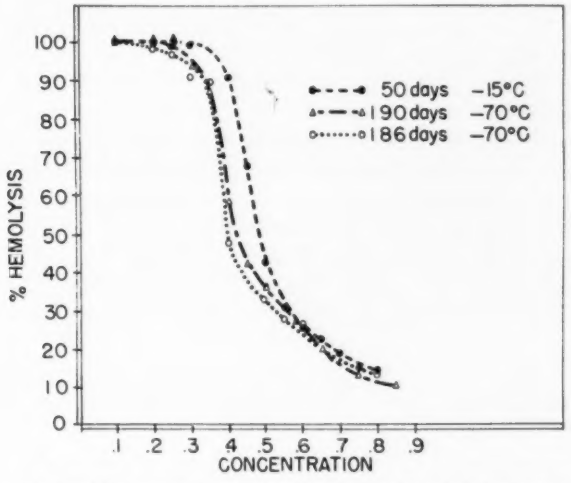

Fig. 6.—Osmotic fragility curves for red blood cell samples taken just prior to transfusion. Note that between 10 and 20% of red cells in each of suspensions hemolyzed during test (one-half hour at 37 C.) in isotonic range of buffered salt concentration. Markedly increased osmotic fragility of these latter cells would indicate osmotic injury during processing or incomplete removal of intracellular glycerin, causing contents of these cells to be hypertonic to isotonic buffered saline, resulting in swelling and hemolysis.

Thus, perhaps, those cells which survive intact through cooling, storage, and rewarming are all capable of normal in vivo survival if all the intracellular glycerin can be removed without cell injury before transfusion. Our data from these experiments are insufficient to answer this question. Certainly, a simple and less time-consuming method for the removal of intracellular glycerin must be found before the use of this low-temperature preservation could be considered practicable. We are hopeful that this problem will be solved by new processing equipment now under study.

Considering both the red cells lost before transfusion and the abnormal loss immediately post transfusion, the over-all survival for the seven bloods stored at

—70 C. up to 6¼ months, ranged from 49 to 90% and averaged 62%. The overall survival for the red cells stored at —15 C. for 50 days was 37%.

Perhaps the most significant finding of these studies was that those stored cells which survived beyond the first 48 to 96 hours post transfusion showed essentially the same in vivo survival as would be expected of fresh red cells.

These observations and those of Mollison and his associates [6] are of special interest, since Blancher and Mayman [17] have shown that the glycolytic rate of red cells previously frozen at —70 C. in glycerin compares favorably with that of fresh red blood cells.

SUMMARY

Seven lots of red cells stored in glycerin solutions at —70 C. up to 6¼ months and one lot of red cells stored at —15 C. for 50 days have been studied as to quantitative recovery after rewarming and removal of glycerin and quantitative in vivo survival after transfusion.

Over 90% of red cells were recovered after subzero storage at —70 C., and approximately 64% of these cells survived normally after transfusion. Of one lot of red cells stored in glycerin at —15 C., 79% were recovered intact, and 47% of these recovered cells survived normally after transfusion. No immediate or delayed reactions were encountered when these stored cells were transfused.

There was evidence from these experiments that a large portion of the abnormal post-transfusion loss of stored cells was due to the incomplete removal of glycerin from some of the cells before transfusion. Other possible methods for the more efficient removal of glycerin have been discussed.

These studies, with those recently reported by British workers, would indicate that the use of glycerin and subzero temperatures may eventually solve the long-studied problem of the prolonged preservation of red blood cells for transfusion purposes.

Dr. G. S. Eadie gave advice, and Barbara Zoellner Gomez, Dr. Alphonse Gomez, George Skipworth, Douglas Johnson, Jeanette Dillon, Grandy Curtis, and Ralph Howse, technical assistance, during the course of these studies.

MICROBIOLOGIC FLORA OF CHRONIC CUTANEOUS ULCERS

In Vitro Sensitivity of Microbiologic Flora to Three Antibiotics, Penicillin, Streptomycin, and Bacitracin

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JOHN W. SOSKA
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THE MICROBIOLOGIC flora of chronic cutaneous ulcers is variable, depending upon the initiating cause of the ulcer and its anatomical location and upon the environment and treatment of the patient. Bacterial infection alone infrequently is responsible for cutaneous ulcers, but once the skin is broken by trauma, trophic changes, or pressure necrosis, an entrance and a fertile medium is provided for bacteria from the environment. By exaggerating necrosis, extending the lesion, and complicating closure, infection adds to the severity and chronicity of cutaneous ulcers.

It is well known that a mixed flora is characteristic of open lesions. The frequency and patterns of occurrence of particular bacterial strains, however, has gained new importance with the availability of antibiotics. A large number of agents which effectively, but quite specifically, inhibit the growth of certain bacteria are available. Topical administration broadens the number of antibiotics and increases the concentrations of these agents which are practicable for use. In the present study the microbiologic flora of chronic cutaneous ulcers observed in the hospital and the in vitro sensitivity of the bacterial strains obtained to the three antibiotics used perhaps most frequently in treatment was determined.

MATERIALS AND METHODS

Sixty-three decubitus ulcers in young persons hospitalized because of paraplegia were utilized as the basis for study. Observations were made over a period of two and one-half calendar years. The study extended over the last six months of 1949 and the first six months of 1950. Cultures were obtained at approximately weekly intervals and in some instances, continuous observations were made for 10 to 12 months. A second period of observation was begun in May, 1951, and continued for six months.

The individual ulcers studied varied somewhat in size, but, in general, they were 4.0 to 6.0 cm. in diameter. Cultures were taken carefully from the base of the ulcers with sterile cotton swabs. These swabs were received in the laboratory within a few minutes after the culture

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material was obtained.[1] The specimens were streaked onto a blood agar plate, an eosin-methylene blue agar plate, an S. S. agar plate, and then inoculated into thioglycollate (Brewer's) broth and brain-heart infusion broth containing 0.03% sodium azide. These primary media were incubated 24 to 48 hours at 37 C. The individual species were identified by colony morphology, staining properties, microscopic appearance, and by biological characteristics upon subculture to appropriate identifying media. The growth in thioglycollate broth after 48 hours was smeared on a glass microslide and Gram stain done.

An individual colony from each of the bacterial types identified was picked up and transferred into tryptose phosphate broth (difco,* pH 7.4) and propagated as a pure culture. Sensitivity to penicillin, streptomycin, and bacitracin was determined routinely by plate dilution technique. Agar Petri plates were prepared freshly for each test, containing antibiotic concentrations of 0.5, 1.0, 5.0, 10, 30, 100, and 200 units or micrograms per milliliter.[2] A 4 mm. loopful of full-grown broth culture was streaked on successive arcs of the antibiotic-containing agar plates, and each series of plates served to test 8 to 12 bacterial strains. Inhibition of growth was observed after 18 to 24 hours of incubation at 37 C. and that concentration of antibiotic which completely inhibited growth was taken as the sensitivity of the test strain.

Eleven anatomical sites were involved. Pretrochanteric ulcers comprised 43% of the total. All but five ulcers (8%) occurred over bony prominences of the pelvic girdle.

TABLE 1.—*Bacteria Cultured From Chronic Cutaneous Ulcers**

Species	No. Times Isolated	Strains Identified, %	Cultures Taken, %	Ulcers Observed, %
Hemolytic Staph. aureus †	162	24	64	70
Micrococcus species ‡	144	21	57	77
Proteus species	86	13	34	49
Pseudomonas species	81	12	32	42
Diphtheroids	73	11	29	52
Group D Streptococcus	59	9	23	27
Esch. coli and paracolon bacilli	33	5	13	33
Aerobacter aerogenes	25	4	10	15
Alpha Streptococcus	7	1	3	6
Achromobacter	4	+	2	6
K. pneumoniae	1	+	+	2

* There were 675 strains from 255 cultures of 63 ulcers.
† Coagulase-positive.
‡ Including Staphylococcus albus.

RESULTS

Microbiologic Flora.—The results of bacteriologic studies are presented in Table 1, with the individual species of bacteria listed according to their frequency of occurrence. The 675 strains isolated during 1949 to 1950 represented more than 16 bacterial species. The most frequently encountered organism was coagulase-positive hemolytic Staphylococcus aureus, which occurred in almost two-thirds of the cultures (63.5%) and involved 70% of ulcers and three-fourths of the patients. Organisms of the genus Micrococcus, including Staphylococcus albus, were the second commonest invaders. They were present in 77% of the ulcers and involved nearly all of the patients. Proteus and Pseudomonas species were present in approximately one-third of cultures and in 49 and 42% of ulcers, respectively. This group

1. Mr. Marvin Aronson gave technical assistance.

2. Penicillin and bacitracin are commonly used on the basis of units, therefore this designation was retained; streptomycin is used on a weight basis, one unit being a microgram. For comparison, 1 unit of penicillin weighs 0.6 γ and 1 unit of bacitracin approximately 25 γ.

and diphtheroid bacilli may be considered the principal bacterial inhabitants of chronic cutaneous ulcers. There was an appreciable difference in the frequency with which these strains and other organisms were encountered.

The Group D streptococci and common Gram-negative coliform bacilli comprise what might be considered a second group of organisms based on the frequency of occurrence. Strains of bacteria from these species were isolated in 10 to 23% of cultures and in from one-third to one-sixth of ulcers.

A comparison of these results with 542 strains isolated in 1951 shows little difference. In the later period there was a relative increase in enterococci and Pseudomonas strains; only slight changes occurred in the incidence of Escherichia coli, Proteus, and staphylococci; strains of Aerobacter aerogenes were recovered less frequently.

A pure culture of a single bacterial strain was found in 20% of the cultures. These were almost always Gram-positive cocci and usually hemolytic Staphylococcus aureus. More than one-half of the cultures taken yielded only one or two bacterial strains. Gram-positive organisms occurred alone in 45% of the specimens studied, whereas Gram-negative organisms rarely occurred alone (Table 2, Chart 1).

Antibiotic Sensitivity Tests.—The in vitro sensitivity for 782 strains of Gram-positive organisms to three antibiotics is shown graphically in Chart 2.

Hemolytic Staphylococcus Aureus, Coagulase-Positive.—Among the strains of hemolytic Staphylococcus aureus studied, only 6% were inhibited by one unit or less of penicillin; one-third of strains were sensitive to 10 units or less; but two-thirds were resistant to 100 units or more. One unit of bacitracin inhibited 31% of strains, and nearly 90% were inhibited by 10 units. One microgram of streptomycin inhibited 29% and 10 γ, 82%; only 10% required 100 γ or more. Thus either bacitracin or streptomycin, which were about equally effective, were far superior to penicillin for inhibiting staphylococci.

Micrococcus Species (Including Staphylococcus Albus).—In 227 strains of micrococci the sensitivity differed from that observed for staphylococci only by a decrease in the number of penicillin-resistant strains and a corresponding increase in those inhibited by concentrations of less than 10 units.

Group D Streptococci.—The largest proportion of 128 strains were inhibited by 1 to 5 units of any of the three antibiotics tested. From 78% (streptomycin) to 90% (bacitracin) of strains were sensitive to 10 units or less. However, 15% of strains were highly resistant to penicillin, which is slightly more than was observed for streptomycin and bacitracin.

Diphtheroid Bacilli.—Penicillin and bacitracin were more effective than streptomycin against 159 test strains. Ten units or less of these two agents inhibited 87 and 82% of strains, respectively, while 10 γ of streptomycin was effective against only two-thirds of the strains.

For all four species, penicillin has a double-peaked distribution curve, with one peak occurring in the range of 1 to 5 units and the other at 100 units or more, thus characterizing the sensitive and resistant strains. With the exception of the staphylococci, the major peak for the Gram-positive organisms is in the sensitive range. Streptomycin and bacitracin show the major peaks for all four species in the sensitive range, and lower peaks for resistant strains occur between 30 and 100 units.

The results of in vitro sensitivity tests of 435 strains of Gram-negative bacilli to penicillin, streptomycin, and bacitracin are shown graphically in Chart 3.

Escherichia Coli.—Among 65 strains tested none was inhibited by 1 unit or less of penicillin; nevertheless, 30% of strains may be said to be moderately sensitive, since 5 to 10 units of penicillin inhibited growth; the remainder were highly resist-

TABLE 2.—*Frequency of Multiple Infection of Cutaneous Ulcers*

	Gram-Positive Only		Gram-Negative Only		Gram-Positive and Gram-Negative	
No. Strains/Ulcer	No. of Cultures	% of Total	No. of Cultures	% of Total	No. of Cultures	% of Total
1	47	18.4	4	1.6	..	...
2	54	21.1	4	1.6	24	9.4
3	14	5.5	0	...	42	16.5
4	1	0.4	0	...	37	14.5
5	0	...	0	...	17	6.7
6	0	...	0	...	8	3.1
7	0	...	0	...	0	...
8	0	...	0	...	3	1.2
Total	116	45.4	8	3.2	131	51.4

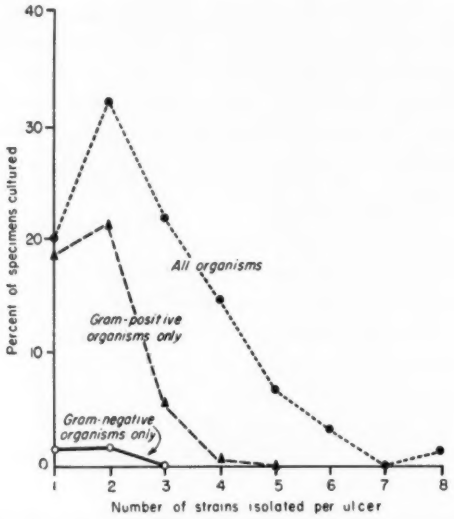

Chart 1.—Character of bacterial infection of chronic cutaneous ulcers (255 cultures of 63 ulcers).

ant. Sensitivity to bacitracin followed a similar pattern. Streptomycin in a concentration of 1 γ per milliliter inhibited 26% of the strains and in 10 γ was effective against 75% of strains.

Aerobacter Aerogenes.—All 36 strains of Aerobacter aerogenes recovered were especially resistant to penicillin and bacitracin. None was sensitive to less than 100 units, and the majority were not inhibited by 200 units of either of these agents. Streptomycin, on the other hand, effectively inhibited 75% of the strains when used

in concentrations of 1 or 5 γ per milliliter, but 22% resisted inhibition by more than 100 γ per milliliter.

Pseudomonas Species.—Penicillin was completely ineffective in a concentration of 200 units per milliliter against 74% of 174 strains, and bacitracin did not inhibit 71% in a concentration of less than 100 units per milliliter. Streptomycin was less

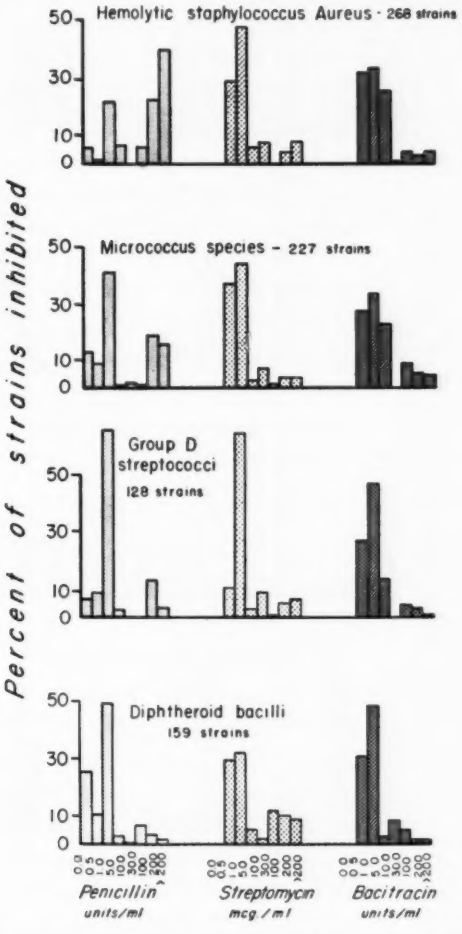

Chart 2.—In vitro sensitivity of Gram-positive organisms to three antibiotics (782 strains from chronic cutaneous ulcers).

effective than was observed against the coliform organisms. Although 60% of strains were inhibited by 10 γ or less, 22% were resistant to more than 100 γ per milliliter.

Proteus Species.—Unlike the other Gram-negative rods, 9% of 160 strains of Proteus species were sensitive to penicillin in a concentration of 1 unit per milliliter, and two-thirds of the strains were effectively inhibited by 10 units. This unusual

sensitivity was not exhibited for bacitracin, which failed to inhibit 90% of the strains in a concentration of less than 100 units per milliliter. Streptomycin inhibited 73% of the strains in a concentration of less than 10 γ per milliliter, and 11% required 10 to 100 γ; 16% were resistant to more than 100 γ.

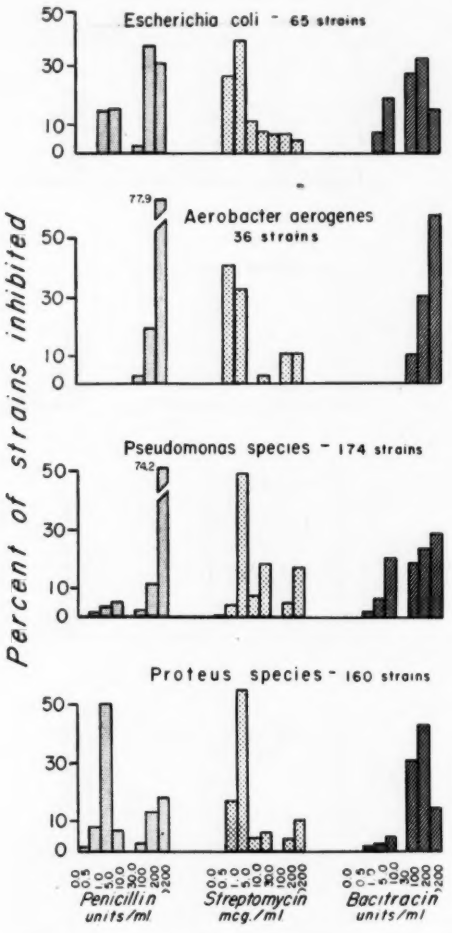

Chart 3.—In vitro sensitivity of Gram-negative organisms to three antibiotics (435 strains from chronic cutaneous ulcers).

The distribution curves of in vitro sensitivity to antibiotics for the Gram-negative species do not show the pronounced double peaks separating sensitive and resistant strains which were observed in the case of Gram-positive organisms, with the exception of Proteus behavior to penicillin and the effect of streptomycin on Aerobacter aerogenes.

COMMENT

It seems noteworthy that in 255 culture specimens taken from 63 chronic cutaneous ulcers and reported here, only 1 or 2 bacterial strains were isolated from more than one-half the specimens. Infection with a single microbial strain, which occurred in 20% of cultures, allows the hope of selecting a specific antibacterial agent with which eradication of the strain may be accomplished. It is likely that elimination of infection is most important in those ulcers in which a single bacterial strain exists. Such a condition commonly represents a virulent pathogenic strain, in this case usually hemolytic Staphylococcus aureus.

Infection of open skin ulcers from contiguous skin and from transmission of infected material from the mucocutaneous orifices of the patient and from his environment. Evans and his associates [3] studied the bacterial flora of normal skin and found that all aerobic bacteria which could be cultured belonged to the Micrococcus species, in which staphylococci were included. Of significant difference in the present data, however, is the frequency with which coagulase-positive hemolytic Staphylococcus aureus was found to be present, in contrast with its occurrence on normal skin.[4] In addition, these strains were predominantly penicillin-resistant. The increasing clinical importance of pencillin-resistant staphylococci has been commented on previously.[5] A high incidence and carrier state of pencillin-resistant staphylococci among hospital patients and personnel also has been observed.[6] Cross infection from these sources obviously is important in cutaneous lesions.[7] The smallest possible number of hospital personnel should attend an open ulcer.

3. Evans, C. A.; Smith, W. M.; Johnston, E. A., and Gilbert, E. R.: Bacterial Flora of the Normal Human Skin, J. Invest. Dermat. **15**:305-324 (Oct.) 1950.

4. Pillsbury, D. M.; Shaffer, B., and Nichols, A. C.: Bacterial Flora of the Normal Skin: Study of Effect of Sulfathiazole and Some Ointment Bases, J. Invest. Dermat. **5**:371-379 (Dec.) 1942. Price, P. B.: The Bacteriology of Normal Skin: A New Quantitative Test Applied to the Study of Bacterial Flora and Disinfectant Action of Mechanical Cleansing, J. Infect. Dis. **63**:301-318 (Nov.-Dec.) 1938. Topley, W. W. C., and Wilson, G. S.: Topley and Wilson's Principles of Bacteriology and Immunity, revised by G. S. Wilson, and A. A. Miles, Ed. 3, Baltimore, Williams & Wilkins Company, 1946. Gillespie, E. H.; Devenish, E. A., and Cowan, S. T.: Pathogenic Staphylococci: Their Incidence in the Nose and on the Skin, Lancet **2**:870-873 (Oct. 21) 1939. Evans.[1]

5. Finland, M.: Present Status of Antibiotics in Bacterial Infections, Bull. N. Y. Acad. Med. **27**:199-220 (April) 1951. Finland, M.; Jackson, G. G.; Kass, E. H.; Haight, T. H., and Womack, C. R.: Some Recent Observations of Staphylococcal Infections in Relation to Antibiotic Therapy, Tr. A. Am. Physicians **64**:343, 1951. Beigleman, P. M., and Rantz, L. A.: The Clinical Importance of Coagulase-Positive, Penicillin-Resistant Staphylococcus Aureus, New England J. Med. **242**:353-358 (March 9) 1950.

6. Dowling, H. F.; Lepper, M. H., and Jackson, G. G.: The Epidemiologic Spread of Antibiotic-Resistant Staphylococci with Measurement of Changes in Sensitivity to Penicillin and Aureomycin, to be published. Barber, M., and Rozwadowska-Dowzenko, M.: Infection by Penicillin-Resistant Staphylococci, Lancet **2**:641-644 (Oct. 23) 1948. Rountree, P.; Barbour, R. G. H., and Thomson, E. F.: Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital, ibid. **1**:435-436 (Feb. 24) 1951. Summers, G. A. C.: Penicillin-Resistant Staphylococci: Distribution Among Outpatients, ibid. **1**:135-141 (Jan. 19) 1952.

7. Cairns, H. J. F., and Summers, G. A. C.: Penicillin-Resistant Staphylococci: Incidence in Relation to Length of Stay in Hospital, Lancet **1**:446 (March 11) 1950. Reiss, E.; Pulaski, E. J.; Amspacher, W. H., and Contreras, A. A.: Penicillin Sensitivity of Staphylococci, New England J. Med. **246**:611 (April 17) 1952.

Results of in vitro sensitivity tests show bacitracin to be most effective of the three antibiotics for Gram-positive organisms. However, topical application in the form of ointment did not eliminate bacitracin-sensitive organisms from some ulcers which were cultured during several months of treatment. In addition, there were instances of an increase during treatment in Gram-negative strains which were not inhibited by bacitracin.

Streptomycin, although usually considered an agent for use in Gram-negative infections, proved to be more effective than penicillin against staphylococci and about equally effective against the other Gram-positive species. However, the rapidity with which resistant strains develop during treatment nullifies much of the apparent value of this drug. Its use is probably best restricted to periods of surgical intervention for closure or grafting, when the antibacterial gains may be maintained by the surgical procedure, and control of infection is essential to their success.

The relatively large number of Proteus strains sensitive to penicillin is a very important observation which is not generally recognized. Coupled with the superiority of streptomycin against the Staphylococcus, it represents a curious inversion in recommendations for use of these agents from earlier days. The recent increase in clinical importance of Proteus infections has nearly paralleled that of the Staphylococcus and is reflected in these results.

Combinations of pencillin, streptomycin, or bacitracin may be valuable, since neither clinical nor laboratory evidence of antagonism has been obtained for any grouping of them. In fact, addition or synergism has been shown in some infections for penicillin with each of the others. On the basis of strain sensitivity to individual antibiotics, rather than synergism studies, it would appear that combining penicillin and streptomycin for use in Proteus infections would decrease by approximately one-half the emergence of preformed resistant strains to each agent.

On the same basis, the addition of penicillin to either streptomycin or bacitracin is not warranted for use in staphylococcic infections, since the number of penicillin-sensitive strains which are resistant to either streptomycin or bacitracin is almost negligible. It cannot be said, however, that penicillin might not delay the emergence during treatment of streptomycin-resistant strains. Bacitracin would appear to supplement streptomycin, but the combined effect, barring synergism, would not be significantly better than with bacitracin alone.

SUMMARY AND CONCLUSIONS

Coagulase-positive, hemolytic Staphylococcus aureus, Micrococcus, Proteus, and Pseudomonas species comprised the principal microbiologic flora of chronic cutaneous ulcers observed in hospital patients. A single bacterial strain was recovered from 20% of cultures, and more than one-half the cultures yielded only two strains. The occurrence of Gram-positive organisms alone was common, but Gram-negative strains alone rarely occurred.

The in vitro sensitivity of 1,217 bacterial strains recovered from cutaneous ulcers was determined for penicillin, streptomycin, and bacitracin. The results are presented for each of the major Gram-positive and Gram-negative species. Only 6% of staphylococci were sensitive to 1 unit of pencillin. Streptomycin and bacitracin

were both more effective. Bacitracin effectively inhibited the majority of Gram-positive strains studied. Streptomycin showed the best over-all effectiveness against both Gram-positive and Gram-negative bacteria. Five units of penicillin inhibited approximately one-half of the strains of Proteus species.

Antibiotic treatment must be used on a clinical and individual basis, with the understanding that open ulcers cannot be kept free of virulent or potentially virulent bacteria for long periods of time, even with effective antibiotics. Treatment therefore should be intensive for short intervals, dictated by bacteriologic cultures and primarily centered around surgical intervention or the need to control extension of the lesion by infection. Antibiotics should not be used for prolonged prophylaxis, since the result is a resistant bacterial flora.

Other implications of the results have been discussed in regard to treatment.

ASCENDING ERECT PHLEBOGRAPHY

Management of Chronic Venous Insufficiency of Lower Extremity

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THE MANAGEMENT of chronic venous insufficiency of the lower extremity, particularly the postphlebitic type, has been the subject of considerable discussion for several years and has in many instances proved to be a perplexing problem to the physician. The various forms of simple or extensive surgical procedures and of local conservative therapy which have been advocated are evidence of the fact that no one type of therapy is adequate in all cases.

A rational approach to the treatment of chronic venous insufficiency must include adequate knowledge of the status of the deep, communicating, and superficial venous systems, with reference to the patency of the venous channels and the competence of the valves. Past history and clinical examination may at times fail to provide an accurate evaluation of the venous return from the lower extremities. We have found ascending phlebography performed with the patient in the erect position to be of considerable value in obtaining this information.

The early attempts at treatment of changes in the lower leg secondary to deep thrombophlebitis were directed at the correction of the local ulceration, if present, and of the varicose veins which frequently follow the episode of thrombosis. In 1916 Homans [1] pointed out that this type of varicosity resulted from the recanalization of the deep veins, with consequent incompetence of their valves and the valves of the communicating veins. He recommended interruption of the communicating veins in the lower leg in the treatment of varicose veins secondary to deep thrombophlebitis. He also advised excision of the ulceration, if present, and subsequent skin grafting in conjunction with removal of the varicose veins.

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1. Homans, J.: The Operative Treatment of Varicose Veins and Ulcers, Based upon a Classification of These Lesions, Surg., Gynec. & Obst. **22**:143-158, 1916.

It was demonstrated in 1937 by Edwards and Edwards [2] that the valves of the deep veins are damaged as a result of thrombosis and that even though the vein may recanalize the valves frequently remain incompetent. Since then, much attention has been directed toward ligation of the deep veins. This was suggested by Homans [3] in 1941. The concept that postphlebitic edema and ulceration are largely the result of long-continued venous stasis and increased venous pressure due to the lack of competent valves in the recanalized deep venous system has thus been developed.

Buxton and his associates [4] in 1944 and in 1945 reported good results with interruption of the superficial femoral vein in patients with long-standing phlebitis. Linton and Hardy [5] in 1947 advocated ligation of the superficial femoral vein and stripping of the saphenous vein. Since then, Gunnar Bauer [6] has recommended ligation of the popliteal vein.

Recently, there has been a trend toward a more conservative management of these patients. The use of properly fitted elastic stockings or elastic bandages, frequent rest periods with elevation of the lower extremities, good foot hygiene, and the advice "to learn to live with your legs" have all been stressed. Certainly it would seem that these measures in conjunction with properly indicated surgical procedures afford the best therapeutic regimen at present.

For the best application of these principles, it is important to have an accurate evaluation of the anatomical and physiological status of the venous system of the involved extremity. Roentgenographic studies of the veins of the leg by the injection of a contrast medium helps considerably in providing this information.

Venograms were first done by Berberich and Hirsch [7] in 1923 and were popularized after the publication by Dougherty and Homans.[8] Interest waned for a few years but was renewed in the last decade with publications by Mark,[9] Mahorner,[10] Felder,[11] and others.

The earlier techniques usually involved injecting the contrast medium into a vein of the foot or ankle, with the patient in the prone or supine position on the

2. Edwards, E. A., and Edwards, J. E.: The Effect of Thrombophlebitis on the Venous Value, Surg., Gynec. & Obst. **65**:310-320, 1937.

3. Homans, J.: Exploration and Division of Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg, New England J. Med. **224**:179-186, 1941.

4. Buxton, R. W.; Farris, J. M.; Moyer, C. A., and Coller, F. A.: Surgical Treatment of Long-Standing Deep Phlebitis of the Leg: Preliminary Report, Surgery **15**:749-756, 1944; Buxton, R. W., and Coller, F. A.: Surgical Treatment of Long-Standing Deep Phlebitis of the Leg: II. A Supplementary Report, Surgery **18**:663-668, 1945.

5. Linton, R. R., and Hardy, I. B., Jr.: Postthrombotic Sequelae of the Lower Extremity: Treatment by Superficial Femoral Vein Interruption and Stripping of the Saphenous Veins (Preliminary Report), S. Clin. North America **27**:1171-1177, 1947.

6. Bauer, G.: The Etiology of Leg Ulcers and Their Treatment by Resection of the Popliteal Vein, J. internat. chir. **8**:937-967, 1948.

7. Bull, D. C.: Phlebography of Lower Extremity, S. Clin. North America **28**:541-544, 1948.

8. Dougherty, J., and Homans, J.: Venography: A Clinical Study, Surg., Gynec. & Obst. **71**:697-702, 1940.

9. Mark, J.: Venography: Its Use in Differential Diagnosis of Peripheral Venous Circulation; Simplified Technic, Ann. Surg. **118**:469-477, 1943.

10. Mahorner, H.: A Method for Obtaining Venograms of the Veins of the Extremities, Surg., Gynec. & Obst. **76**:41-42, 1943.

11. Felder, D. A.: A Method of Venography, Radiology **54**:516-520, 1950.

x-ray table. Other techniques required that the patient be placed in the Trendelenburg position, with a tourniquet at the groin to direct the contrast material into the deep veins. In general, these methods failed to give good visualization of the deep venous system because of incomplete filling. Moreover, the presence or absence of competent valves in the deep and communicating veins became a matter of conjecture, since the antigravity or functional mechanism of the valves is not tested with the patient in either the horizontal or Trendelenburg position.

Retrograde phlebography has been advocated by Luke [12] and Shumacker,[13] who inject the dye into the femoral vein at the groin. Bauer [14] surgically exposes the

Fig. 1 (Case 1).—Patent deep veins, including anterior tibial, posterior tibial, popliteal, and superficial femoral, are well demonstrated by the radiopaque medium and are shown to be adequately supplied with anatomically intact and functional valves. Circles indicate two such valves. In addition, incompetent communicating veins between superficial and deep systems and associated superficial varicosities are demonstrated. Entrance of abnormally dye-filled lesser saphenous vein (horizontal arrow) into popliteal vein is demonstrated. Note large incompetent perforating veins (vertical arrow) between anterior tibial vein and lesser saphenous vein.

12. Luke, J. C.: Retrograde Venography of the Deep Leg Veins, Canad. M. A. J. **49**:86-88, 1943.

13. Shumacker, H. B.: Symposium on Recent Advances in Surgical Physiology: The Surgical Physiology of Peripheral Vascular Disorders, Clin. North America **29**:1683-1697, 1949.

14. Bauer, G.: Patho-Physiology and Treatment of Lower Leg Stasis Syndrome, Angiology **1**:1-8, 1950.

femoral vein at the groin and, through a catheter introduced into the distal portion, injects the contrast medium, with the foot of the x-ray table lowered. Another method of threading a catheter through the short saphenous vein into the deep system has been described.[15]

Martin and McCleery [16] in 1950 described an improved method of ascending phlebography with the patient in the supine position, using an ankle tourniquet and a blood pressure cuff on the lower thigh.

At this hospital we have adopted the method of ascending phlebography with the patient in the erect position, as described by Scott and Roach [17] in 1951, of the Johns Hopkins University School of Medicine. During the past year this pro-

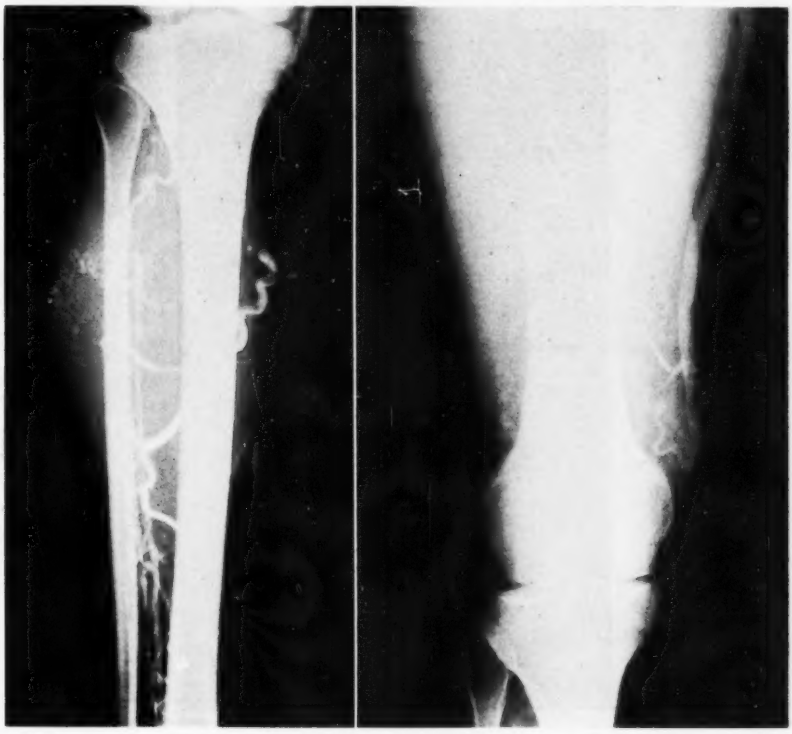

Fig. 2 (Case 2).—Irregular web or lace-like appearance of deep veins, best visualized between osseous structures just below knee, indicates previous thrombosis with subsequent recanalization and destruction of valves. Few deep veins in leg are patent. Only distally are several valves seen. Abnormal collaterals shunt blood into superficial veins. Greater saphenous vein, in which normal valves are demonstrated proximally, transports nearly all of venous return from extremity.

15. Ferreira, J. A.; Villamil, E. J. F., and Ciruzzi, A. O.: Dynamic Phlebograph, Angiology **2**:350-373, 1951.

16. Martin, R. S., and McCleery, R. S.: An Improved Method of Venography for the Preoperative Evaluation of the Postphlebitic Extremity, Surgery **28**:322-341, 1950.

17. Scott, H. W., Jr., and Roach, J. F.: Phlebography of the Leg in the Erect Position, Ann. Surg. **134**:104-109, 1951.

cedure has been performed in 75 patients. These patients, with few exceptions, represented definite problems in the evaluation of deep venous circulation. In all these patients the information obtained was of value either on the basis of positive or of negative findings. In several instances the roentgenographic information differed from the impression gained by history and clinical examination. It should be emphasized that when doubt as to the completeness of the clinical information exists, the findings from phlebography will be of value.

TECHNIQUE

The patient is placed on the x-ray table, which is elevated to an angle of 75 to 80 degrees. The patient stands on the foot rest with the leg to be studied in the midportion of the table.

Fig. 3 (Case 3).—Complete obstruction of all deep veins is demonstrated. Recanalization has not yet occurred. Venous return is accomplished by means of superficial systems of veins, as shown by dye-filled tributaries of greater saphenous vein. Many superficial veins are dilated and tortuous, and a few normal valves, such as one circled, are visualized.

The leg is internally rotated 25 degrees to minimize superimposition of bony and vascular structures. A tourniquet is placed just above the ankle and tightened sufficiently to obstruct the superficial venous system.

A No. 20 gauge needle is then inserted into a vein on the dorsum of the foot and is held in place with adhesive tape. The needle is connected by a short piece of rubber or plastic tubing to a syringe containing 25 or 30 cc. of 35% iodopyracet (diodrast®). The contrast medium is then injected rapidly, but not forcibly, over a period of 5 to 10 seconds. X-rays are then taken of the leg and of the lower thigh and, if indicated, of the entire thigh. When the capacity of the

venous bed appears to be increased by the existing pathology, a greater volume of iodopyracet (30 to 50 cc.) is used. These x-rays can be taken without haste because with the patient in this erect position the contrast medium leaves the venous channels of the leg rather slowly.

Patients are tested for sensitivity to iodopyracet by the intradermal skin test and are further checked by injecting 1 cc. of the contrast medium at the beginning of the phlebographic procedure and waiting a few seconds before completing the injection. There have been several instances of transient syncope prior to the injection of iodopyracet. These are due to a combination of psychic factors related to the various aspects of the procedure. A mild urticaria following the injection was noted in one patient. No other reactions have been encountered.

This method of phlebography provides satisfactory filling of the deep venous system of the leg and demonstrates the presence or absence of competent valves. The abnormal pattern resulting from recanalization of a thrombosed vein is readily detectable. With the tourniquet firmly

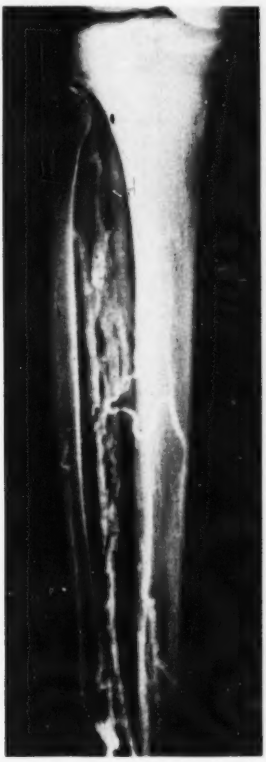

Fig. 4 (Case 4).—Deep veins, although patent, are somewhat irregular and tortuous, and typical lace-like appearance of recanalization following thrombosis is seen in upper portion of leg. However, segments of anterior and posterior tibial groups of deep veins in lower three-fourths of leg are seen to be adequately supplied with functional valves. Only a few abnormal communicating channels are visualized.

applied at the ankle, the iodopyracet is directed from the venous network of the dorsum of the foot into the deep veins of the leg, and no contrast medium appears in the superficial veins unless the valves of the perforating veins are incompetent.

This procedure has been helpful to us in the evaluation of postphlebitic sequelae and in other instances of chronic venous insufficiency of the lower extremities. The following cases illustrate its usefulness.

CASE 1.—T. L. H., a 37-year-old woman, had a history of large varicose veins of several years' duration. There was no definite history of previous deep vein thrombosis. Clinical examination revealed large varicosities over the right lower extremity. Tourniquet tests suggested that the venous insufficiency was based on incompetency of the valves of the superficial veins and of several communicating veins and that the deep venous system was patent. These findings were confirmed by phlebography (Fig. 1). The x-rays demonstrated adequate filling of the deep veins well up into the thigh, with normally functioning valves. This patient was treated by ligation and stripping of the greater and lesser saphenous veins and ligation of the incompetent perforating veins.

Fig. 5 (Case 5).—Deep veins are devoid of valves. Deep veins just below knee and popliteal and anterior femoral veins (arrow) present characteristic features, previously illustrated, of recanalization following thrombosis with destruction of valves. Note abnormal network of dilated tortuous collateral and superficial veins about knee.

CASE 2.—J. C. L., a 35-year-old white man, had an acute thrombophlebitis of the left leg in 1945, with secondary pulmonary embolism. A ligation of the superficial femoral vein on the left was done at that time. Since then he has had swelling, ulceration, and recurrent bouts of cellulitis in his left lower leg. Clinical evaluation indicated impairment of the deep venous system, but the extent of this damage could not be determined. The phlebogram revealed that the venous circulation was from the patent deep veins distally, through large communicating veins into the greater saphenous system, and, to a smaller degree, into the lesser saphenous system (Fig. 2). The deep veins above this showed evidence of recanalization with destruction of

valves. Several functional valves were seen in the greater saphenous system. This case illustrates the marked degree of impairment in the deep veins and the attempt at recanalization.

A popliteal ligation was carried out and some early improvement was noted. A segment of the popliteal vein showed recanalization of an old thrombus.

CASE 3.—F. S., a 35-year-old white man, had a history of bilateral acute thrombophlebitis with bilateral superficial femoral vein ligations 5½ years ago. He has continued to have chronic edema and pain in both legs. The phlebograms bilaterally show complete absence of deep circulation. All the contrast medium is visualized in the superficial veins (Fig. 3). The extent of deep venous involvement in this instance could not have been adequately determined by clinical evaluation, and an operative procedure for ligation of the popliteal or other deep veins would have been a useless procedure.

This patient was fitted with full-length elastic stockings and treated conservatively.

CASE 4.—C. R. B., a 25-year-old white man, had a history of bilateral thrombophlebitis seven years ago. He now has pain, edema, and large varicosities. The phlebogram showed the anterior and posterior tibial groups of veins to be well visualized but more tortuous and irregular than normal (Fig. 4). A few functioning valves could be seen in spite of the evidence of previous thrombosis. Several incompetent communicating veins were also noted. The popliteal vein was not adequately filled, and recanalization of that structure is suggested. This case demonstrates that occasionally some valvular function is retained or regained after deep vein thrombosis. From this information, surgical therapy directed at the superficial and communicating veins, with the postoperative use of elastic bandages and other conservative measures, was warranted. Again, the extent of deep vein impairment could not have been adequately determined by clinical evaluation, for, in view of the history and of the clinical findings, considerable impairment of the deep circulation would be expected.

CASE 5.—J. H. B., a 32-year-old white man, had bilateral superficial femoral vein ligations seven years ago after a pulmonary embolus. The phlebogram showed evidence of recanalization following thrombosis, with complete absence of the valves of the deep veins and poor visualization of the popliteal and superficial femoral veins (Fig. 5). Several large incompetent communicating veins and numerous superficial veins were visualized. Because of other illnesses, no surgery has been done on this patient.

COMMENT

The valves of the deep veins of the legs are damaged as a result of thrombosis, and even though recanalization occurs the valves may remain incompetent. Malfunctioning deep valves lead to orthostatic venous overloading and stasis, for the blood, forcibly squeezed out and poured toward the heart by the contractions of the striped muscle masses of the leg, is allowed to backflow by incompetent valvular structures.[14] This phenomenon certainly plays a part in the production of chronic venous insufficiency in the postphlebitic patient, although, presumably other factors are also of significance.[15] Bauer believes that the rational treatment of the postphlebitic lower extremity with recanalization of deep veins is to block the large deep trunk at the popliteal region by resection. The blood then squeezed out of the lower leg would seek collateral pathways and not backflow and assemble distally.

Active treatment of the patient with varicose veins presupposes a knowledge of the state of the deep veins. As stated previously, clinical examination, as well as past history, may at times fail to provide information as to whether a state of venous insufficiency is primary or postphlebitic in nature. We have found that phlebography is of great value in this determination. In addition to providing a satisfactory method of deep vein evaluation, phlebography by the technique outlined has been of considerable value in demonstrating incompetent communicating

18. Højensgård, I. C.: Phlebography in Chronic Venous Insufficiency of the Lower Extremity: Preliminary Report, Acta radiol. **32**:375-339, 1949.

veins between the superficial and deep systems. We believe that this method of phlebography has allowed us to use a more rational approach to a difficult problem.

Our experience with phlebography performed with the patient in the horizontal position was not satisfactory. Not infrequently incomplete filling of the veins, low intensity of roentgenographic contrast, and poor visualization of valvular structures were found. Phlebography with the patient in the erect position, which tests the antigravity or functional mechanism of the valves, has produced maximal distention of the valve sinuses and high intensity of the contrast. We agree with Højensgård that from the standpoint of pathology, it is immaterial through which venous pathways the blood flows when the patient is in the horizontal position, since chronic venous insufficiency gives symptoms only when the patient is in the erect position where hydrostatic phenomena are manifest.[18] Ascending phlebography with the patient in the erect position seems to offer the most practicable and physiologic method yet devised for the roentgenographic examination of the patient with chronic venous insufficiency of the lower extremity. Information of both anatomical and functional significance is obtained which allows a rational choice of surgical procedures.

We do not think that this procedure is necessary or justified in the usual case of varicose veins of the extremity. It is indicated, however, in cases in which there is a definite history of deep thrombophlebitis or in those in which there is any doubt concerning the status of the deep venous system. It is useful in varicosities when the cause may depend upon the presence of complete or of incomplete deep venous obstruction. Certainly, this method of visualizing the venous system is frequently helpful in varicose vein problems that have been previous surgical failures. As has been shown in the cases reported, the history and clinical findings alone in some of these patients may very well lead to the employment of a useless or, sometimes, a harmful surgical procedure. The value of phlebography in these difficult cases is that it helps provide complete information which forms the basis for rational therapy in chronic venous insufficiency of the lower extremity.

SUMMARY

Chronic venous insufficiency of the lower extremity and some of the problems of management are discussed.

The value of ascending phlebography, with the patient in the erect position, in outlining rational therapy in difficult cases is demonstrated.

Several illustrative cases are presented.

INTESTINAL OBSTRUCTION RESULTING FROM BILIARY CALCULI (GALLSTONE ILEUS)

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HARRY H. JACOB, M.D.
AND
JACK A. CANNON, M.D.
LOS ANGELES

THE COMMONEST entry of biliary calculi into the intestinal tract is by way of a cholecystoenteric fistula. However, a choledochoenteric fistula and, when the stones are small enough, the ampulla of Vater also serve as pathways.[1] Fistulization between the biliary and intestinal tracts occurs as a complication of either cholecystitis caused by a calculus [2] or a perforating gastric or duodenal ulcer which penetrates the gall-bladder wall.[3] The present series deals with seven instances of the former condition, which occurred in six patients at the Harbor General Hospital.

With the establishment of the fistulous tract, any stones trapped within a distended inflamed gall bladder find their escape into the intestinal tract and thus relieve the acute obstructive cholecystitis.[4] If, as usually happens, the calculi are of a small diameter, as compared with the intraluminal diameter of the narrowest portion of the intestinal tract, the stone will pass out through the rectum without further complications.[3] If, however, this relationship between the diameter of the calculus and the intestinal lumen does not exist, the stone or stones become impacted along their course, and acute intestinal obstruction, commonly referred to as "gallstone ileus," results. Since the lumen of the small bowel gradually narrows in diameter as it approaches the cecum, it is not unusual that the commonest point of occlusion is in the terminal ileum.[5]

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1. Rigler, L. G.; Borman, C. N., and Noble, J. F.: Gallstone Obstruction: Pathogenesis and Roentgen Manifestations, J. A. M. A. **117**:1753 (Nov. 22) 1941.

2. (*a*) Harvey, S. C., and Conner, G. J.: Intestinal Obstruction Due to a Gallstone: Report of Unusual Incidence, Yale J. Biol. & Med. **14**:501 (May) 1942. (*b*) Wangensteen, O. H.: Intestinal Obstructions, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1947, p. 316.

3. Bockus, H. L.: Gastroenterology, Philadelphia, W. B. Saunders Company, Vol. 3, 1946, p. 700.

4. Haggstrom, G. A., and Rousselot, L. M.: Acute Intestinal Obstruction, S. Clin. North America **30**:479 (April) 1950.

5. (*a*) Balch, F. G., Jr.: Gallstone Ileus, New England J. Med. **218**:457 (March 17) 1938. (*b*) Moore, R. A.: Textbook of Pathology: Pathologic Anatomy in Its Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease, Philadelphia, W. B. Saunders Company, 1944, p. 836. (*c*) Wangensteen.[2b]

The term gallstone ileus is used by some authorities to designate any intestinal obstructive phenomenon, dynamic or adynamic, occurring as a result of biliary tract pathology. Categorically, the term gallstone ileus, we believe, should be reserved for those instances of mechanical intestinal obstruction resulting from actual obturation by biliary calculi.

In the past, we have been led to believe that the occurrence of gallstone ileus was rather rare. In recent years, however, it has been shown that although the incidence of this condition is quite low, it is by no means rare. Haggstrom and his associates [4] report an incidence of 7% in a series of 76 cases of acute intestinal obstruction, while Hinchey reports an incidence of 6%.[6] Gallstone ileus is further reported by many observers as occurring in approximately 0.3 to 0.5% of all cases of cholelithiasis.[7]

The present series of patients comprises 5% of the 136 instances of acute intestinal obstruction in which operation or autopsy was carried out at the Harbor General Hospital during the three-year period from January, 1949, to January, 1952.

The average mortality rate resulting from gallstone ileus, as reported in the literature, varies from 30 to 70%.[8] In the series reported by Haggstrom and Rousselot,[4] a 25% mortality rate is reported. The average mortality rate is high, evidently as a result of the following factors: (*a*) the advanced age of the patients affected by the disease [9]; (*b*) the obesity coincidentally associated with this and other biliary tract pathology [10]; (*c*) the frequency of masking symptoms referable to the biliary system [5a]; (*d*) the lack of awareness of the relatively common incidence of this condition,[7] and (*e*) the associated water and chemical imbalance which generally increases the operative risk in any type of acute bowel obstruction.[2b] All of these contributing factors result in a delay in diagnosis, preoperative preparation, and surgical intervention.[8]

In this study, complete recovery occurred in four out of seven instances of gallstone ileus, presenting a mortality rate of 29%.

Women are much more prone to have obstruction resulting from gallstones in the intestinal tract than are men.[11] The ratio of intestinal obstruction due to biliary calculi is reported as high as 16 women to 1 man.[2b] All patients in this series were women.

The average age of our patients was 86 years. The youngest patient in the series was 67 years old and the oldest, 93. It must be remembered, therefore, that the diagnosis of gallstone ileus should be considered in all cases of small bowel obstruction encountered in elderly women who have not had a previous abdominal operation.[11]

6. Hinchey, P. R.: Gallstone Ileus, Arch. Surg. **46**:9 (Jan.) 1943.

7. (*a*) Mayo, C. W., and Brown, P. W.: Intestinal Obstruction Caused by a Gallstone, Surgery **25**:924 (June) 1949. (*b*) Moore.[5b]

8. (*a*) Downing, W. L.: Gallstone Ileus: Report of 5 Cases, J. Iowa M. Soc. **38**:95 (March) 1948. (*b*) Hinchey.[6] (*c*) Rigler.[1]

9. Bockus.[3] Wangensteen.[2b]

10. Hinchey.[6] Downing.[8a]

11. Balch.[5a] Hinchey.[6] Mayo.[7a]

As previously stated, the point at which the gallstone is likely to become impacted along its trip through the intestinal tract is the terminal ileum.[12] In three of the seven instances of gallstone ileus in this report, the stone was impacted in the terminal ileum; in three it was in the jejunum, and in one it was in the sigmoid colon.

The history, symptomatology, and physical findings attendant upon the diagnosis of gallstone ileus are characterized only by their lack of consistency. The symptoms of crampy abdominal pain, nausea, vomiting, and abdominal distention associated with constipation progressing to obstipation, consistent with obstruction in the lower portion of the small bowel, are seen in this disease. The insidiousness of onset of symptoms, the history of old cholecystic disease in elderly women, and an absence of findings typical of other specific causes of intestinal obstruction are suggestive of gallstone ileus. The very incongruity of findings is suggestive of the diagnosis, as is shown in the following case presentations.

In most instances of intestinal obstruction due to gallstones, there is a definite history of previous cholecystic disease.[13] On occasion the diagnosis is further suggested by the presence of gallstones in the emesis.[14] Rarely, a large gallstone can be felt in a loop of small bowel by digital palpation through the rectum. This coincidence was encountered in the unusual first case in our series. The visualization of air in the biliary tree by means of a flat film of the abdomen is diagnostically significant in instances of either a cholecystoenteric or choledochoenteric fistula. This finding in association with obstruction of the small bowel should establish the diagnosis. This case of recurrent gallstone ileus demonstrates the importance of a careful physical examination, including digital examination of the rectum, as well as the imperativeness of a complete exploration of the abdominal contents at the time of operation.

REPORT OF CASES

CASE 1.—This 93-year-old white woman was first admitted to the surgical service on May 15, 1951, complaining that for two days she had had cramping abdominal pain, nausea, and coffee-ground vomiting, associated with abdominal distention. The patient had no bowel movements nor did she pass flatus per rectum for three days prior to admission. There was no history of a previous operation or symptoms of gall-bladder disease.

Physical examination revealed a thin, elderly, afebrile woman with a soft, but moderately distended, lower abdomen. Loops of distended small bowel were visible through the thin unscarred abdominal wall. Some peristaltic rushes were heard initially, but later the abdomen became silent. There was light direct and indirect rebound tenderness in the lower abdomen. Rectal and pelvic examinations were noncontributory.

A flat film of the abdomen disclosed small bowel loops under moderate tension with "step-laddering," and air was demonstrable in the biliary tree, significant of cholecystoenteric fistula [1] (Fig. 1). Sigmoidoscopy to 10 in. (25 cm.) and barium enema were nonrevealing. Suction via a Harris tube was instituted; parenteral fluids and large doses of antibiotics were administered in an effort to prepare the patient for early celiotomy.

Two days after admission, exploration, with use of local anesthesia, was performed, with a preoperative diagnosis of gallstone ileus.

A 3 by 2.5 cm. faceted and laminated gallstone was found obstructing the lower jejunum. By means of jejunotomy the stone was removed, and the bowel was closed by the method of Heineke-Mikulicz. The patient's condition was considered critical during the abdominal closure.

12. Wangensteen.[2b] Haggstrom.[4] Moore.[5b]

13. Balch.[5a] Hinchey.[6]

14. Harvey.[2a] Wangensteen.[2b] Bockus.[3]

During the postoperative period the patient's condition improved considerably. Oral feedings were started six days after operation and progressed satisfactorily. She passed flatus per rectum and had bowel movements.

Ten days after operation, the abdomen once again became distended. The patient was thoroughly reexamined. Loops of distended small bowel could once again be seen outlined beneath the thin abdominal wall, and a picture of obstruction of the small bowel, similar to the previous episode, was present. A rectal examination was performed in the course of the reevaluation. A faceted hard mass 3 cm. in diameter was palpated through the rectal wall in a loop of small bowel lying in the left pelvic region. The mass was palpable in the same position on repeated examinations.

A flat film of the abdomen was consistent with mechanical obstruction of the small bowel.

Fig. 1.—Roentgenogram showing pattern of distended small intestines under moderate tension. Air can be seen outlining biliary tree, indicating fistulization between biliary and intestinal tracts. No radiopaque stone is seen (Case 1).

On the 12th postoperative day reexploration revealed a gallstone 3 cm. in diameter impacted in the distal ileum. Another smaller stone was found intraluminally 12 cm. proximal to the first.

Initially the patient's postoperative course was satisfactory, but the situation was complicated by a cerebral vascular accident. Hypostatic pneumonia developed, and she died 10 days after her second bout of gallstone ileus. Consent for autopsy could not be obtained.

Case 2.—This 78-year-old white woman was admitted to the hospital on July 21, 1949, with a 40-year history of cholecystic disease and one episode of associated jaundice.

Three weeks prior to the present admission the patient had onset of anorexia and epigastric pain which radiated through her back. The pain continued intermittently with increasing severity for four days, at which time she began having green-colored emesis. Nausea and

vomiting continued until the time of admission. Past history revealed that intolerance of fatty food was prominent. She underwent a salpingo-oophorectomy and appendectomy in 1909. The remainder of the history was noncontributory.

Physical examination of this elderly woman revealed marked dehydration, tympanitic distended abdomen with hyperactive bowel sounds, and diffuse rebound tenderness. Her temperature was 97.8 F. and pulse rate 60 beats a minute. A leucocyte count of 17,100 was reported. A flat film of the abdomen revealed a radiopaque density measuring 3 by 6 cm. located in the upper left side of the abdomen, with distention of a loop of small bowel and the stomach visible proximal to the point of density [15] (Fig. 2).

Intestinal intubation with suction was established, and fluid parenterally and antibiotics were administered. No flatus was passed per rectum during the next several days of observation.

Nine days after admission surgical intervention was undertaken. A preoperative diagnosis of gallstone obstruction in the proximal portion of the small bowel was made. On exploration

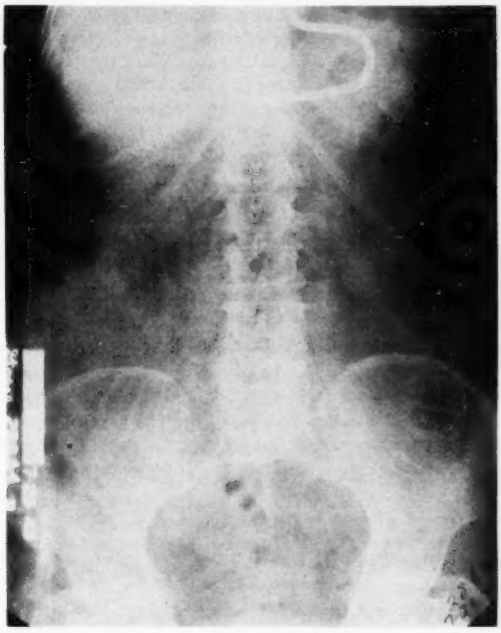

Fig. 2.—Roentgenogram demonstrating 3 by 5 cm. oval homogenous density with faintly outlined calcific border, appearance of which is consistent with large gallstone. Air and fluid distended loops of small bowel are scattered throughout abdomen. One centimeter below first stone, 1.5 centimeter stone with heavier calcific border is seen (Case 2).

the gall bladder was found to be covered and bound down by the omentum, a fibrinous exudate, and numerous adhesions. Two large gallstones measuring 4 by 3 cm. and 2 by 3 cm., respectively, were palpated 3 ft. (91 cm.) distal to the ligament of Treitz. Distal to the obstruction the bowel was collapsed. The stones were removed through a longitudinal incision in the jejunum proximal to the point of obstruction. The jejunum was closed transversely in two layers.

The patient pursued an uneventful postoperative course and was asymptomatic when discharged on the ninth postoperative day.

15. Nemir, P.: Gallstone Ileus: Report of 8 Cases, Surg., Gynec. & Obst. **94**:469 (April) 1952.

When the case was reevaluated three years after operation, the patient stated that she had managed to keep relatively asymptomatic only by restricting her diet to nonfatty foods.

CASE 3.—This 75-year-old white woman was admitted to the surgical service on Dec. 13, 1950. She presented a history of nausea and vomiting, repetitious in nature, having its onset five weeks prior to admission. One month prior to admission, after cholecystography and upper gastrointestinal roentgenography, exploration was performed at another hospital. A cholecystoduodenal fistula was closed and a cholecystectomy performed. Intermittent vomiting persisted after this procedure, and the patient's feces continued clay-colored during the postoperative period. Seven days after operation, bile-colored drainage was seen coming from the incision.

On the day of admission to the Harbor General Hospital this woman was acutely ill, markedly dehydrated, and mentally confused. The abdomen was mildly distended, and the right epigastric incision was disrupted and undermined with bilious drainage flowing freely from the excoriated wound.

Nasogastric intubation with continuous suction was established. The water and electrolyte imbalance was remedied by administration of fluids parenterally. The excoriated necrotic wound margins which were undergoing proteolytic destruction were treated with applications of aluminum hydroxide gel. With the use of a U-shaped glass tube with multiple perforations, continuous sump suction of the bilious drainage from the wound was maintained. Over a period of two or three weeks the drainage gradually diminished and finally ceased.

At this time, gross blood was seen returning from the Levin gastric suction tube. Simultaneously, thrombophlebitis developed in the patient's left leg. Because of the gastrointestinal bleeding, the usual anticoagulant therapy was deferred. Topical thrombin and aluminum hydroxide gel were instilled through the Levin tube at hourly intervals, and massive antibiotic therapy was instituted. The patient's condition improved.

The onset of abdominal pain, distention, and obstipation prompted complete reevaluation. The rectal ampulla was empty; a flat film of the abdomen revealed distended loops of small bowel, and the remainder of the physical examination confirmed a diagnosis of acute obstruction of the small bowel of unknown origin.

Forty-one days after admission, exploration revealed a large gallstone, 2.5 by 5 cm., impacted in the distal ileum. The calculus was removed by means of an ileotomy. Multiple adhesions and fistulae were noted between loops of small bowel. A segment of ileum at the site of three large fistulae was resected, and an end-to-end anastomosis was performed.

The immediate postoperative course was stormy, and the patient died in peripheral vascular collapse on the first postoperative day. Permission for postmortem examination could not be obtained.

CASE 4.—This 67-year-old white woman was admitted to the surgical service on Feb. 2, 1950, complaining of intermittent cramping abdominal pain that had been present for two days. This symptom was associated with repeated bouts of nausea and vomiting, which persisted until the time of admission.

The patient stated that a right radical mastectomy had been performed for carcinoma six years previously. No history of disease of either the gastrointestinal or biliary tract or recurrence of the breast lesion was obtainable.

On admission this somewhat obese well-developed woman was observed to be vomiting coffee-ground-like material. Her abdomen was obese and somewhat distended, without surgical scars or discernible hernias. Bowel sounds were inaudible except for peristaltic tinkles that were heard coincident with the bouts of cramping pain. On rectal and pelvic examination no abnormalities were revealed. A scar on the right side of the chest and absence of the right breast were the only other positive physical findings.

A flat film of the abdomen in the supine position revealed one loop of distended small bowel. No gas was seen in the colon.

A leucocyte count of 17,000, with 85% neutrophiles, accompanied blood chemistry reports which were consistent with dehydration alkalosis. The patient was treated with fluids parenterally, nasogastric suction, and antibiotics.

Fifteen hours after admission, abdominal exploration was performed. A preoperative diagnosis of small bowel obstruction of unknown cause was made. Approximately 4 ft. (121

cm.) distal to the ligament of Treitz, a 2.5 by 3.7 cm. gallstone was found obstructing the jejunum. Jejunotomy, removal of the obturating calculus, and closure of the bowel after the manner of Heineke-Mikulicz were carried out.

Two days following operation, bowel sounds were audible, gastric suction was discontinued, and the patient was taking liquids orally.

The early postoperative course of the patient was complicated by pneumonitis. On the sixth postoperative day, thrombophlebitis developed in the left leg. Treatment consisted of the administration of heparin, bishydroxycoumarin (dicumarol*), and aureomycin. The patient was discharged fully recovered 19 days after operation.

By means of correspondence we have managed to find that after discharge it was necessary for this patient to undergo a cholecystectomy at another hospital.

CASE 5.—This 80-year-old white woman was admitted to the medical service on Aug. 8, 1950, complaining of crampy periumbilical pain and abdominal distention which had persisted for 24 hours. These symptoms were associated with belching and bilious vomiting. Obstipation and inability to pass rectal flatus were noted for a total of 48 hours prior to hospital entry. A long-standing history of fatty food dyscrasia was obtained. The patient was transferred to the surgical service, where it was noted that at the time of the colicky periumbilical pains the silence of the distended abdomen was interrupted by peristaltic rushes. Intestinal intubation and hydration measures were begun.

A flat film of the abdomen was characteristic of small bowel obstruction. A barium enema revealed a normal large bowel, but at the terminal ileum a nonopaque egg-shaped mass, interpreted as a gallstone, was outlined by barium (Fig. 3).

On the 11th hospital day, celiotomy was performed for gallstone ileus. A 3 by 9 cm. biliary calculus was found in the terminal ileum. Distally, the bowel was collapsed and proximally, the small intestine was distended. By means of a longitudinal incision proximal to the obstructing point, the stone was milked back and removed. The ileotomy was closed transversely.

On the third postoperative day, the patient's abdomen was flat and soft and she was being given oral feedings. On the ninth postoperative day, she was discharged, fully recovered.

When the case was reevaluated two years after her operation, this patient was found to be totally asymptomatic and did not have to adhere to any special diet.

CASE 6.—This 78-year-old white woman was admitted to the hospital on Oct. 12, 1950, with crampy abdominal pain, nausea, vomiting, and a history of similar episodes occurring intermittently for the preceding 16 months. These bouts had been accompanied by chills and fever and associated with dark-colored urine and clay-colored stools.

During previous hospitalization, a diagnosis of cholelithiasis, esophageal diverticulum, and a large diverticulum of the descending duodenum was made.

On physical examination this emaciated elderly woman was afebrile, jaundiced, dehydrated, and appeared chronically ill. The abdomen was soft and scaphoid. There was generalized upper abdominal tenderness, and a small cystic mass was palpable in the right upper quadrant. The liver edge was two fingerbreadths below the right costal margin. Aside from an elevated icteric index, all liver function tests were reported essentially normal.

Hydration measures were taken, and numerous unsuccessful attempts were made to ascertain the cause of the jaundice. The epigastric distress persisted and became progressively severe.

Twenty-nine days after admission, exploration was performed. A chronically inflamed gall bladder containing many calculi and a thick-walled common duct measuring 1.5 cm. in diameter were seen in association with a choledochoduodenal fistula. A firm biliary calculus measuring 2.5 by 1.5 cm. was impacted in the sigmoid colon. It was possible by means of extraluminal manipulation to force the stone into the rectum. A cholecystectomy and exploration of the common duct were performed. The postoperative period was rather stormy, but at the time of discharge, 16 days after operation, the patient was asymptomatic.

The patient could not be reached for follow-up study, but according to reports from close relatives, she is totally asymptomatic at the time of this writing, 29 months after operation.

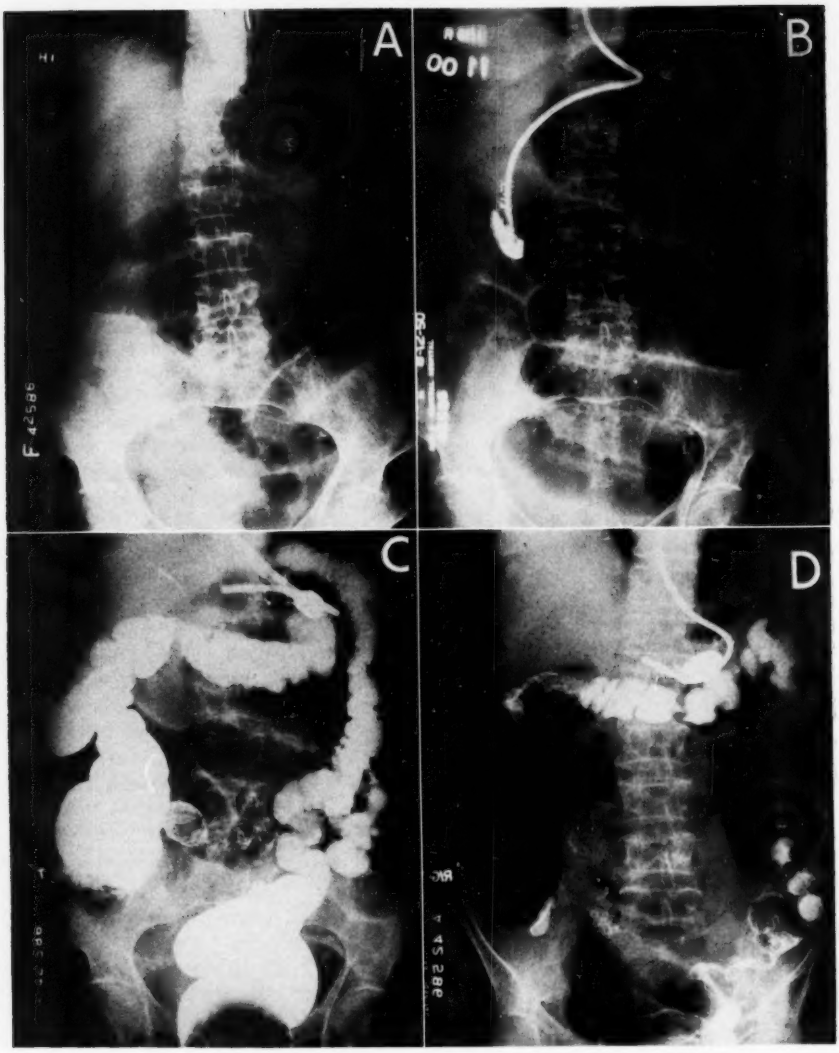

Fig. 3.—Series of roentgenograms showing changes taking place during hospital course of one patient (Case 4). *A*, typical picture of small bowel obstruction, showing distended loops of small intestine, without gas in rectum, as seen on admission. Neither biliary calculi nor free air is seen in biliary tree. *B*, findings of small bowel obstruction have increased in spite of intestinal intubation. Obstructing level now appears to be in terminal ileum. *C*, barium enema outlines colon, which has numerous diverticuli. Large 3 cm. gallstone just proximal to ileocecal valve, with distended small bowel loops proximal to obstruction, is seen. *D*, postevacuation films show absence of major portion of opaque material, but stone is outlined by coating of barium.

COMMENT

The uniqueness of Case 1 is self-evident. Numerous implications can be derived from an analysis of the course of events. Since each bout of intestinal obstruction by biliary calculi had widely variant features, it should be analyzed individually. In Case 1 a provisional diagnosis of gallstone ileus was made without a history of gall-bladder disease. The diagnosis was suggested by the fact that this elderly woman, with classic small bowel obstruction, had not had a previous abdominal operation and that roentgenograms showed air in the biliary tree, characteristic of cholecysto-enteric fistulization (Fig. 1). In the second bout of gallstone ileus, a calculus was palpated transrectally in a loop of small bowel. In the light of the previous history, with a mechanical small bowel obstruction at the terminal ileum, as shown by barium enema, this diagnosis could not be excluded. If proximal exploration of the small bowel had been performed at the time of the original celiotomy, when the faceted obstructing stone was extracted, the second calculus, which became impacted in the narrow terminal ileum 10 days later, might have been revealed. On the other hand, the second stone may not have left the biliary tract until shortly before the second obstruction occurred.

It has been suggested that faceted biliary calculi found intraluminally in the intestine are indicative of another stone still present proximally in the intestinal tract or in the gall bladder.[16] As has been shown in this case, if such a calculus is permitted to remain behind, gallstone ileus, on rare occasions, does recur. It may therefore be concluded that if the obstructing agent is found to be a faceted gallstone a careful palpation of the gall bladder is mandatory at the time of operation. If stones are palpable within the gall bladder, a cholecystostomy with removal of the calculi, which present a potential source of recurrent gallstone ileus, is indicated. If stones are not palpated within the gall bladder, exploration of the intestine proximal to the point of obstruction is indicated. This case apparently represents the 11th instance of recurrent gallstone ileus to be reported in the literature.[17]

In Case 5 a positive preoperative diagnosis was made as a result of finding no abdominal scars, a past history of typical biliary disease, a barium enema which demonstrated the obstructing gallstone, and physical findings compatible with obstruction of the small bowel. This case emphasized the importance of permitting the reflux of barium proximal to the ileocecal valve during the performance of a barium enema when the diagnostic possibility of gallstone ileus is being considered.

Case 6 in our series is interesting in view of the fact that it is impossible to determine how many of the symptoms were due to the cholecystic disease and how many could be attributed to the gallstone ileus. The overshadowing gall-bladder disease could well have caused many of the symptoms by virtue of associated adynamic ileus. The increased severity of the symptoms just prior to operation could be explained on the basis of a temporary mechanical intestinal obstruction.

Follow-up studies of the patients in our series suggest that in the majority of instances an interval cholecystectomy is indicated if symptoms of gall-bladder disease persist. This operation can be performed at an optimum time after the relief of the gallstone ileus. If a faceted stone is found obstructing the intestine, and a matching

16. Wangensteen.[2b] Nemir.[15]

17. Noskin, E. A., and Tannenbaum, W. J.: Recurrent Gallstone Ileus: Case Report, Surgery **31**:599 (April) 1952.

stone is located in the gall bladder, a cholecystostomy is indicated. Such a procedure at the time of the relief of the intestinal obstruction may render the patient asymptomatic for many years, and the hazards of a further operative procedure may not be warranted.

SUMMARY

The term "gallstone ileus" is defined as any instance of mechanical obstruction which results from obturation by biliary calculi. The pathogenesis of gallstone ileus, which results from fistulization between the biliary and intestinal tracts in cases of chronic cholelithiasis, is discussed.

In recent years the condition has been diagnosed more frequently and therefore has been found to occur oftener than was previously thought.

The mortality rate in this condition is relatively high. Contributing factors to the high mortality rate are (*a*) advanced age of patients; (*b*) obesity coincidentally associated with this and other biliary tract disease; (*c*) frequency of masking symptoms referable to the biliary system; (*d*) lack of awareness of the relatively common incidence of this condition, and (*e*) associated water and chemical imbalance.

Early surgical intervention after adequate preoperative preparation followed by careful postoperative management is the only method by which the high mortality rate can be reduced. Early diagnosis is a necessity and is possible only if one is aware of the findings suggestive of gallstone ileus. A thorough history and physical examination along with roentgenographic studies are important diagnostic aids.

Seven instances of gallstone ileus occurring in six women who were treated in the surgical service of the Harbor General Hospital are reviewed. One of these patients was surgically relieved of two bouts of intestinal obstruction due to gallstone obturation and apparently represents the 11th case of recurrent gallstone ileus to appear in the literature.

Follow-up studies have been made on the four patients who remain alive at the time of this writing, and the studies indicate that any patient who survives an attack of gallstone ileus may have further symptoms and may require corrective operation.

These seven instances of gallstone ileus represent 5% of all proved cases of small bowel obstruction at this hospital during a three-year period. The mortality rate in this series was 29%.

Summary of Data on Cases of Gallstone Ileus

Case No.	Sex	Age, Yr.	Previous Gall-Bladder Symptoms	Not Diagnosed Prior to Operation	Preoperatively Diagnosed: History	X-Rays	Physical Examination	Location of Calculus	Outcome
1 (1st instance)	F	93	None	..	X	X (Abdominal findings)	X	Jejunum	Recovered
1 (2d instance)	F	93	None	..	X	X (Rectal examination)	X	Ileum	Died
2	F	78	Definite	..	X	X	..	Jejunum	Recovered
3	F	75	None	X	..	..	..	Ileum	Died
4	F	67	Definite	X	..	..	..	Jejunum	Recovered
5	F	80	None	..	X	X	..	Ileum	Recovered
6	F	78	Definite	X	..	..	..	Sigmoid	Recovered
Averages.....		78½	43%	43%					

Total instances of gallstone obturation 7
Mortality rate 29%

A correct preoperative diagnosis was made in five of the seven instances of small bowel obstruction due to biliary calculi. Only four of the six patients had a history of previous gall-bladder disease.

CONCLUSIONS

Gallstone ileus occurs more commonly than was previously believed. Early diagnosis and surgical intervention are the only methods of reducing the high mortality rate. This complication of neglected gall-bladder disease can be avoided only if earlier operation for cholelithiasis is performed.

The diagnosis of gallstone ileus should be considered in all cases of small bowel obstruction encountered in elderly women who have had no previous abdominal operation.

Only by careful evaluation of the history and physical findings and by using all the available laboratory aids and roentgenography can an accurate and early diagnosis of small bowel obstruction due to biliary calculi be made.

If a faceted stone is found obstructing the intestine, a matching stone should be sought in the gall bladder. If such a stone is found, a cholecystostomy with removal of the stone should be performed. If the matching biliary calculus is not located in the gall bladder, the proximal small bowel should be explored.

Unless contraindicated by grave surgical risk, an interval cholecystectomy is recommended in cases in which symptoms from the diseased gall bladder continue.

SLOWLY ABSORBED TUBOCURARINE CHLORIDE IN ORTHOPEDICS

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WASHINGTON, D. C.

ONE OF the most difficult and universal problems in the management of musculoskeletal injuries is that of overcoming muscle spasm. Spasm accompanies almost every type of skeletal injury, causing the patient considerable pain and limitation of motion and interfering with the efforts of the physician to correct skeletal abnormalities. The attempts of orthopedists to relieve muscle spasm indirectly by the use of narcotics, immobilization, heat, and other agents leave much to be desired.

The capacity of curare to relax skeletal muscle directly has been known since the early descriptions of the paralytic effect of South American Indian poison arrows. In the past two decades considerable progress has been made in purifying and studying the active curare principle both pharmacologically and clinically.[1] Relatively pure preparations of tubocurarine chloride are now commercially available and dosage schemes based on aqueous solutions of 3 mg. per cubic centimeter, which cause only minor side-effects, have been developed for use principally in conjunction with anesthetics and shock therapy.

The limitation to the wider use of tubocurarine chloride imposed by the use of aqueous solutions was recognized in 1941, particularly for neuromuscular disturbances, in which the relaxing action of curare appeared desirable for instances of long-standing spasm and for spasticity. Bennett,[2] who had seen the potentialities of the drug in certain neuromuscular disorders, commented on the desirability of having available a safe and long-acting curare preparation. The shortcomings of the earlier preparations in peanut oil and beeswax (4.8%) were overcome by suspending highly purified tubocurarine in a suspending medium of peanut oil, oxycholesterol derivatives, and a smaller amount of beeswax (2%). Such a preparation offers the advantages of the muscle relaxing effects without subjecting the recipients to the hazard of intercostal paralysis, while at the same time providing greater physical stability and greater convenience for the user. I shall use the term "tubadil" to distinguish this preparation from the aforementioned type.[3]

"Tubadil" is administered intramuscularly. It exerts a more gradual and prolonged relaxing effect on the skeletal muscle spasm than that obtained by giving repeated doses of aqueous tubocurarine chloride solutions or of the previously mentioned suspension.

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1. McIntyre, A. R.: Curare: Its History, Nature, and Clinical Use, Chicago, University of Chicago Press, 1947.

2. Bennett, A. E.: Clinical Investigations with Curare in Organic Neurologic Disorders, Am. J. M. Sc. **202**:102 (July) 1941.

3. "Tubadil," manufactured by Endo Products, Inc., contains in each cubic centimeter 25 mg. d-tubocurarine pentahydrate in a base of peanut oil, oxycholesterol derivatives, and beeswax, 2%.

Fuller [4] reported that this repository preparation of pure tubocurarine chloride could safely give more prolonged relief than can be provided by morphine and morphine-like substances for pain associated with muscle spasm due to traumatic injuries. Hoback [5] confirmed the findings of Fuller. A more recent report by Fuller [6] states that the preparation can be safely administered to presurgical patients in a dose of 2.5 cc. (62.5 mg. tubocurarine chloride) per 70 kg. of body weight.

While my experience and that of others has proved the safety of this form of tubocurarine chloride, an objective basis to account for the clinical safety has become available only recently. Moyers [7] reported that when "tubadil," in doses of 0.5 mg. of the alkaloid per pound of body weight (highest dose 90 mg., or 3.6 cc., "tubadil"), was given preoperatively to patients ready to undergo abdominal and thoracic surgery, plasma level determinations showed that a level of about 1 γ of tubocurarine chloride was not exceeded. This is in contrast to plasma levels obtained when aqueous solutions of tubocurarine chloride were administered intravenously, the usual route of administration. Pittinger, Morris, and Cullen [8] showed that intravenous administration resulted in a "spiked" curve, much as one would expect. The highest concentration appeared within the first 10 minutes after injection and frequently approached levels which threatened respiratory paralysis.

As is well known, respiratory hazard is associated with the use of high concentrations. One may appreciate the difference between the repository form of tubocurarine chloride used with aqueous solutions by the following statement:

> It was noted that spontaneous intercostal activity did not resume in any subject while plasma concentration of the drug was three micrograms or greater; however, this plasma level may not represent a critical level in this respect.

"Tubadil," as reported by Moyers, gives a slow rise to a level of about 1 γ per milliliter of plasma and remains at that level for a considerably longer time than when the drug is given in water. Obviously 90 mg. of tubocurarine chloride in aqueous solution would not be given at one time or during one operation. Undoubtedly, it is this slow release of the alkaloid to levels lower than intercostal paralyzing levels which accounts for its safety and usefulness in the type of orthopedic spasms dealt with in this report.

In passing, other items of Moyer's unpublished report may be of interest because of the comparatively larger doses used in his series than by us. "Tubadil" appeared to be well tolerated; respiratory failure did not occur; muscular relaxation was satisfactory, and the postoperative demand for narcotic analgesics appeared to be reduced by almost one-half.

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4. Fuller, J. D.: Use of Slowly Absorbed Suspension of D-Tubocurarine Chloride in Traumatic Injury, J. A. M. A. **143**:789 (July 1) 1950.

5. Hoback, W. W.: Repository Tubocurarine in Trauma, J. Tennessee M. A. **45**:16 (Jan.) 1952.

6. Fuller, J. D.: Advantages of the Preoperative Use of Slowly Absorbed D-Tubocurarine, Anesthesiology **13**:370 (July) 1952.

7. Moyers, J.: The Role of Muscle Spasm in the Production of Postoperative Pain, read before the Fifth Annual Postoperative Assembly in Anesthesiology, New York, Dec. 8, 1951.

8. Pittinger, C. B.; Morris, L. E., and Cullen, S. C.: D-Tubocurarine Chloride Concentrations in Human Plasma After Intravenous Injection During Anesthesia, J. Lab. & Clin. Med. **38**:397 (Sept.) 1951.

I have already reported on the treatment of low back pain with aqueous solutions of tubocurarine chloride.[9] In the current series to date, over 543 doses of "tubadil" have been administered to 149 orthopedic patients exhibiting severe degrees of muscle spasm. These results are summarized in the accompanying Table.

The following discussion concerns the factors which this experience has shown to be important in the successful application of this new therapeutic tool to orthopedic problems. Six illustrative cases will be presented.

INDICATIONS, DOSAGE, AND EFFECTS OF "TUBADIL"

Orthopedic Indications.—A prime indication for the use of "tubadil" is the relief of striated muscle spasm. Thus in fractures, sprains, back injuries, and other conditions accompanied by painful spasm, long-acting tubocurarine chloride repre-

Summary of Data

Type	No. of Cases	No. of Injections	Average No. of Injections	Results		% Improved
				Satisfactory	Unsatisfactory	
Shoulder conditions						
Bursitis, calcareous tendinitis, bicipital tendinitis, scapular arm syndrome, rotator cuff injuries, fractures of neck	12	34	3.0	9	3	67.0
Hip conditions						
Arthritides, dislocation, trochanteric bursitis, iliotibial band syndromes, tuberculosis, fractures	31	183	6.0	26	5	83.5
Back						
Acute low back syndrome	42	143	3.4	38	4	90.9
Chronic low back syndrome	24	81	3.4	18	6	75.0
Fractures	3	17	6.0	3	0	100.0
Acute upper back and posteervicodorsal syndromes	8	26	3.3	5	3	62.5
Torticollis, acute, spasm	6	17	3.0	6	0	100.0
Torticollis, upper back and shoulders	4	20	5.0	1	3	25.0
Fractures						
Excluding hip, shoulders, and back	19	32	1.7	11	8	57.8
Total	149	543	3.6	117	32	78.5

sents a direct attack on a major problem. When painful somatic conditions are unrelated to spasm, such as some instances of neuritis or neuralgia, tubocurarine chloride is not likely to be of much value.

The larger the muscle bulk involved in spasm, the better the response to curare. Thus involvement of an area like the wrist, which is primarily tendinous and ligamentous, is not as dramatically relieved by "tubadil" as are the large muscle bulks of the back, hips, thighs, and shoulders. Relief of spasm with "tubadil" is frequently a most helpful adjunct to traction and manipulative procedures.

In acute muscle injuries, "tubadil" is most effective. However, in cases of chronic inflammatory myofibrositis or arthritis, little can be accomplished with curare as long as the etiologic factor remains active.

Curare is contraindicated for any one suspected of having myasthenia gravis. Other than this I have found no contraindications, although in the earlier literature it was advised that the drug should be used with caution in the presence of pulmonary and renal disease.

9. Lipow, E. G.: Symptomatic Relief of Low Back Pain, M. Ann. District of Columbia **19**:682 (Dec.) 1950.

Dosage.—The average safe and effective dose of "tubadil" for ambulatory patients is about 1.0 cc. Individual responses vary, and effective responses have been obtained with as little as 0.5 cc., while some subjects require 2.5 cc. Muscle relaxation following intramuscular injection is noted in 15 to 45 minutes and lasts for many hours. I have limited the number of injections to one within 18 hours, although Fuller [6] has given up to 2.5 cc. of "tubadil" preoperatively with no signs of respiratory embarrassment. If necessary, he repeated the same dose at 24 hours. No evidence of a cumulative effect has been noted.

It is our impression that, pound for pound, persons with more fat and less bulk require doses 20 to 25% larger in order to achieve the same effect obtained in a lean muscular subject. The emotional make-up of the patient is a factor contributing to muscle tone and, consequently, must be considered in deciding on the dose of curare. Occasionally, small doses of aqueous tubocurarine chloride (about 6 mg.) may be given intramuscularly for an immediate effect, which is then maintained by giving an average dose of "tubadil."

Untoward Reactions.—The side-effects of "tubadil" are less frequent and less severe than those of aqueous curare. The difference between the therapeutic dose and the unsafe paralyzing dose is very great. This may be accounted for by the studies on blood levels previously mentioned.

In my experience with over 543 therapeutically effective doses of "tubadil," I have not had a single reaction which required tracheotomy or artificial respiration. Diplopia and some incoordination may occur in about 15% of the recipients following the administration of relatively large doses. For this reason, patients treated on an ambulatory basis are not permitted to drive their own cars after receiving curare. These minor symptoms are transitory and require no countermeasures.

As a precaution against severe toxicity, which may result from accidental overdose, it is wise to keep available the limited antidote neostigmine (prostigmin®) and a source of oxygen, although I have not had to resort to such measures.

REPORT OF CASES

Case 1 (Hip Fracture).—Mrs. J. F. Mc., a 63-year-old married woman, sustained a fracture of the neck of the left femur. She was immediately brought to a physician's office and then hospitalized. When examined at the hospital, she was found to have a marked amount of spasm, shortening of the left limb, and other characteristics of hip fracture. Skin traction was applied (about 15 lb. [7 kg.]) for three days, during which time the spasm was not perceptibly diminished, although the leg shortening was somewhat reduced. The patient was restless, complained considerably of pulling, nagging, and drawing sensations in the left leg, and required continuous doses of codeine and, occasionally, of morphine. She could not sleep in spite of rather large doses of secobarbital (seconal®). Twelve hours preoperatively 1.5 cc. of "tubadil" was given. About four hours later the patient experienced considerable relief and volunteered the information that she was no longer aware of the pull on her leg, although the weight was still hanging. Examination at this time showed a ½ in. (1.2 cm.) lengthening of the femur. That night the pain was entirely alleviated, and she had her first night of restful sleep, the use of codeine and morphine having been discontinued. The bone was subsequently pinned with a Smith-Petersen nail and McLaughlin plate, with uneventful recovery. The operation was facilitated by the complete relaxation of the patient. In the opinion of the anesthetist the amount of thiopental (pentothal®) sodium and gas-oxygen needed for good anesthetic effect was considerably lowered. "Tubadil" therapy was continued postoperatively for three days,

and no narcotic or analgesic agents were necessary except for secobarbital at night for restlessness. She was discharged from the hospital on the seventh postoperative day with no further medication except for mild sedation.

CASE 2 (Acute Torticollis).—Mrs. L. D., aged 36, some two years previously, Jan. 3, 1949, had suffered an acute torticollis immediately after putting on a blouse over her head. She was given aqueous tubocurarine chloride (3 mg per cubic centimeter) and applications of heat and had complete amelioration of symptoms in four days. However, during this regimen, she was confined to her bed. Since that time she had been in good health and had had no recurrence until April 10, 1951, when after a mild upper respiratory infection she suddenly turned her head and was unable to straighten it. Upon examination the head was found tilted to the right; there was spasm present of the right trapezius, right sternomastoid, and right posterior cervical muscles.

"Tubadil," 1.0 cc., was given intragluteally, followed by diathermy and 25 lb. (11 kg.) of head traction. This same procedure was repeated the following day. On the third day, only slight stiffness was noted and "tubadil" was discontinued. The patient was apparently well on the 4th day. The patient continued in her work as telephone operator during the entire course of treatment. There have been no recurrences.

CASE 3 (Fracture of First Lumbar Vertebra).—Mrs. L. S., aged 52, was seen Nov. 9, 1951, one week after a fall on her buttocks. She stated she "felt something snap" and immediately had rather severe pain in the lower portion of her back, worse on sneezing and coughing. This pain radiated to the buttocks. She had a slight lordosis. Forward bending was sharply limited, and all motions of the spine, however slight, gave rise to pain. She had been unable to sleep since this injury. Palpation and percussion of the spine elicited marked pain and tenderness over the first, second, and third lumbar vertebrae, and there was severe spasm of the erector spinae muscles. X-rays revealed a compression fracture of the first lumbar vertebra.

The patient was admitted to Georgetown University Hospital and put in mild hyperextension. Sedation was obtained with codeine and barbiturates. The day after admission 1.5 cc. of "tubadil" was given intragluteally, and some four hours later she experienced marked relief. The spasm was notably less severe. Hyperextension of the spine was increased, being facilitated by daily doses of "tubadil" (1.5 cc.). She remained quite comfortable, and five days after admission a body cast was applied. It was not necessary to continue "tubadil" after the second day following application of cast. She made an uneventful recovery and is now employed as credit manager in a large department store. There were no noticeable side-effects during the administration of "tubadil," except for drowsiness.

CASE 4 (Calcareous Tendinitis).—J. F. H., aged 31, was seen Nov. 5, 1951, at which time he stated that two days previously while putting up a shelf he began to have severe pain in the right shoulder, which increased in severity and was now so intense that he was unable to raise his arm or to put on his coat. A history of repeated right shoulder pain, attributed to an old baseball injury and lasting for short intervals over the past four years, was obtained. Examination showed marked tenderness in the right subacromial bursa region, tenderness over the insertion of the right supraspinatus muscle, and marked limitation of abduction, internal rotation, and flexion of the right humerus. X-rays showed a typical calcific deposit in the region of the insertion of the right supraspinatus tendon.

A regimen of multiple procaine hydrochloride injections, diathermy, hot packs, support, and sedation gave some improvement, but in view of the spasm now apparent in the shoulder and humeral muscles, "tubadil" (1.7 cc. intramuscularly) was given daily in conjunction with the other therapy. The patient improved rapidly and on the fourth day, pendulum exercises and "wall-climbing" were begun. He was entirely symptom-free in two weeks.

CASE 5 (Myofibrositis).—Mrs. M. C., aged 48, was seen first on June 26, 1950. At that time she suffered a fractured coccyx and also complained of pain in the upper part of her back, particularly between the scapulae and over both shoulders. This pain, with no particular radiation, was worse in the morning and after rest. X-rays showed a fracture of the coccyx and a mild hypertrophic arthritis of the cervical and dorsal spine, with no encroachment on the neural foramina. Examination showed marked pain and angulation of the coccyx, tenderness, and fibrositic nodules of both supraspinatus groups of muscles and in the erector spinae

groups, while there were tenderness and pain in both infraspinatus groups. Complete work-ups at George Washington University Hospital were noncontributory to other conditions, and the patient was given a regimen of physical therapy, salicylates, and mild sedation. The coccygeal fracture responded to treatment immediately, but there was no improvement in the condition of the back and shoulders. "Tubadil," in doses of from 1.0 to 2.0 cc. intramuscularly, given daily gave no relief. This was discontinued after seven days and the patient was sent home. Again "tubadil" therapy was resumed with the addition of mephenesin (tolserol®) to the schedule, but without appreciable relief. She was referred to another physician, who at that time tried corticotropin, with some relief of the shoulder and back discomfort. She is still under treatment for this condition.

CASE 6 (Recurrent Backache).—Miss J. H., a 19-year-old student, had suffered from recurrent backaches since going away to school. The last previous attack of backache was treated at another clinic, where she was told she had a "disc," but surgery was not recommended at that time. She was hospitalized for two months and wore a brace for another two months before the backache disappeared. The present backache began two days previously, after packing and carrying her luggage and driving 600 miles. The attack was, in her own words, "exactly the same as the other, and hurt just as much." The pain was aggravated by sneezing and coughing but was not shooting or lightning-like in character. Roentgenograms were essentially negative, except for a slight narrowing between the fourth and fifth lumbar vertebrae. The patient was able to stand on both feet reasonably well but had considerable difficulty in changing position. The right gluteal fold was lower than the left. The lower limbs were normal, the pelvis was level, and posture was good. The upper part of her back was movable, while the lower part was fixed. Spasm was demonstrable throughout the length of the spine. Raising the leg straight and stretching the hip were painful on the left side, indicating a sciatic component. Accordingly, paravertebral block with procaine was done at the fourth and fifth lumbar vertebrae, with considerable relief from the sciatic symptoms. However, the backache continued, although somewhat less intense. "Tubadil" (1.5 cc.) was then administered. Two hours after the first dose, the patient felt she could sit up in bed. "Tubadil" was given once daily for five days. By the end of the week she was symptom-free. No brace has been worn, and she continues to be asymptomatic.

COMMENT

It must be brought out that in the tabulated cases "tubadil" was used only to alleviate muscle spasm. The proper concomitant treatment was given for each condition. However, patients in whom muscle spasm was the predominant factor and in whom the underlying etiologic factor of spasm was either bypassed temporarily or not discovered (as in some of the low back syndromes) "tubadil" was the only drug used.

SUMMARY

"Tubadil," a slowly absorbed preparation of tubocurarine chloride, has been found to be effective in alleviating muscle spasm, which accompanies many orthopedic conditions, when the dosage, described in the body of the report, is not exceeded in either quantity or frequency of injection.

It is longer and smoother-acting than aqueous solutions of tubocurarine chloride and results in fewer side-effects. Mild symptoms of curarization, such as diplopia and skeletal muscle incoordination, are transient and disappear in the course of several hours. However, it must be emphasized that the suggested dosage and interval between injections be not exceeded.

Its orthopedic indications are discussed and illustrated.

LEIOMYOSARCOMA OF THE DUODENUM

Report of a Case and Summary of the Literature

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OF ALL the duodenal tumors, the leiomyosarcomata are the rarest. After a thorough search of the literature, only 27 such tumors have been recorded, making the present case summary the 28th leiomyosarcoma of the duodenum to be published. However, it is not only the rarity of the disease that prompts the report of this additional case, but also the confused picture exhibited by the roentgenograms and the clinical symptoms. Von Salis,[1] in 1920, was the first to report a case of leiomyosarcoma of the duodenum. All cases published since that time have been carefully reviewed and are cited in this paper, thus bringing the surgical literature up-to-date for this disease.

Pathologists differ as to the origin of these tumors. Some believe that leiomyosarcomata are a transformation from the benign leiomyomata, while others maintain that they are malignant from the outset (Ewing). The tumor originates in the muscular layer of the duodenum and grows either into the lumen or onto the outside of the intestinal wall. Such growth outward may occur without any distortion of the lumen, thus permitting adequate patency of the intestinal canal. However, the usual finding is a combination of growth outward with some protrusion into the lumen and with eventual ulceration through the intestinal mucosa. Most of the leiomyosarcomata reported have demonstrated a central necrosis with an expulsion of necrotic contents into the intestinal tract, sometimes accompanied by blood. This was evident in our case as a bloody diarrhea. The sizes of these leiomyosarcomata have been reported from 2.5 cm. in diameter to that of an adult head. However, the commonest size has been that equal to a fetal head. These tumors are malignant and metastasize locally, as well as throughout the liver. Metastases have been described that spread diffusely throughout the patient's body.

The complications of duodenal leiomyosarcomata are readily understood if one bears in mind the regional anatomy where the tumor originates. The duodenum is a retroperitoneal portion of the intestinal tract and in intimate relation with the pancreas. Adjacent to it are the superior mesenteric vessels and the mesentery of the colon. As the duodenal tumor enlarges, it may encroach upon any of these structures, including other parts of the small bowel and the colon. Posterior growth is also possible, involving the vena cava and the kidneys. In the case to be reported herewith, the tumor originated in the third portion of the duodenum and involved

1. von Salis, H. W.: Über das Sarkom des Duodenum insbesondere das Myosarkom, Deutsche Ztschr. Chir. **160**:180-204 (Dec.) 1920.

the superior mesenteric vessels and their branches. The middle colic, right colic, and ileocolic vessels were in intimate relationship with the tumor, and the portion of the intestinal tract supplied by them had to be sacrificed.

The symptoms are dependent upon the duodenal site of origin of the tumor, and its progressive growth. A large leiomyosarcoma may obstruct the duodenum or biliary tract with the resulting symptoms. Degeneration of the tumor with necrosis and erosion of the mucosa may result in anemia and the finding of blood and a purulent mucous discharge into the bowel. Perforation into the peritoneal cavity has been known to occur. On the other hand, the whole clinical picture may be confused because of widespread metastases throughout the body.

A study of the reported cases permits one to state that a typical history is as follows: A 35- to 65-year-old person of either sex complains of weight loss, weakness, anemia, and possibly abdominal pain. A mass in the abdomen may or may not have been noticed. Usually, there has been some blood noted in the stools, often a bloody diarrhea. Roentgenology has usually been very helpful in making the diagnosis. If the tumors are sufficiently large, they will be seen in the flat plate. After erosion into the lumen and fistulization, barium may be seen to enter the tumor. Of course, a laparotomy insures an accurate and complete diagnosis.

The only treatment is surgical; at operation it may be necessary to resect all or part of the pancreas and a portion of the small and large intestines. The patient concerning whom this present report is made required a block resection of the portion of duodenum from which the tumor arose, the removal of 3 ft. (91 cm.) of terminal ileum, appendix, cecum, ascending colon, and right transverse colon, including the accompanying blood vessels adherent to the tumor.

REPORT OF A CASE

L. S., a 54-year-old white man, was admitted to the Boulevard Hospital on March 10, 1952, complaining of abdominal pain, weakness, fatigue, and weight loss. Concerning his past history, he related that in October, 1951, he noticed a bloody diarrhea, following which he was admitted to a hospital. The hemoglobin was 10 gm. per 100 cc.; roentgenograms were taken, and he was told upon discharge six days later that he had "an internal pile that ruptured." However, his condition became progressively worse, with increasing anemia, weakness, fatigue, thirst, and cramps in the upper abdomen. Since January, 1952, his wife had noticed a lump in his abdomen. Fever was never present. There was a 20 lb. (9 kg.) weight loss up to the time of his present hospital admission.

Physical examination revealed a man who had lost some weight but who did not appear extremely ill. Examination of the heart and lungs was essentially negative, as was the rest of the physical examination, except for that of the abdomen. A palpable mass was present to the right of the midline and particularly in the upper part. The mass was firm, slightly tender, but fixed and not easily movable. The admission blood count showed a slight anemia; hemoglobin 10.5 gm. per 100 cc.; red cell count 4,000,000; leucocytes 11,900 (88 polymorphonuclear leucocytes, 2 young forms, 11 lymphocytes, and 1 eosinophile). The urine examination was essentially negative.

Roentgenographic findings were based upon prone and supine films taken 10 minutes after barium was swallowed. The stomach and pylorus appeared to be normal except for some pylorospasm. The descending limb of the duodenum described an "S" curve with some coarsening of the mucosal folds. The mucosal markings of the transverse duodenum were faintly outlined but without any abnormality. However, there was a broad convexity upward of the transverse duodenum, indicating pressure from below. Proceeding downward from the junction of the descending duodenum with the horizontal portion of the duodenum, and 1½ in. (3.8 cm.) apart, were two narrow pathways containing barium. They both led to a pseudopodic amor-

phous collection of barium about 2 by 1½ in. (5.0 by 3.8 cm.). Our impression was that this collection of barium with its pathways did not exhibit any of the characteristics of intestinal mucosa, thereby indicating that all of this barium was external to the small or large bowel.

A laparotomy was performed March 14, 1952, with the patient under fractional spinal anesthesia. A large soft mass 8 in. (20 cm.) in diameter was found attached to the third portion of the duodenum. The wall of the mass itself was similar in appearance to the adjacent duodenum and unquestionably arose from this viscus. The pedicle of attachment was about 2 in.

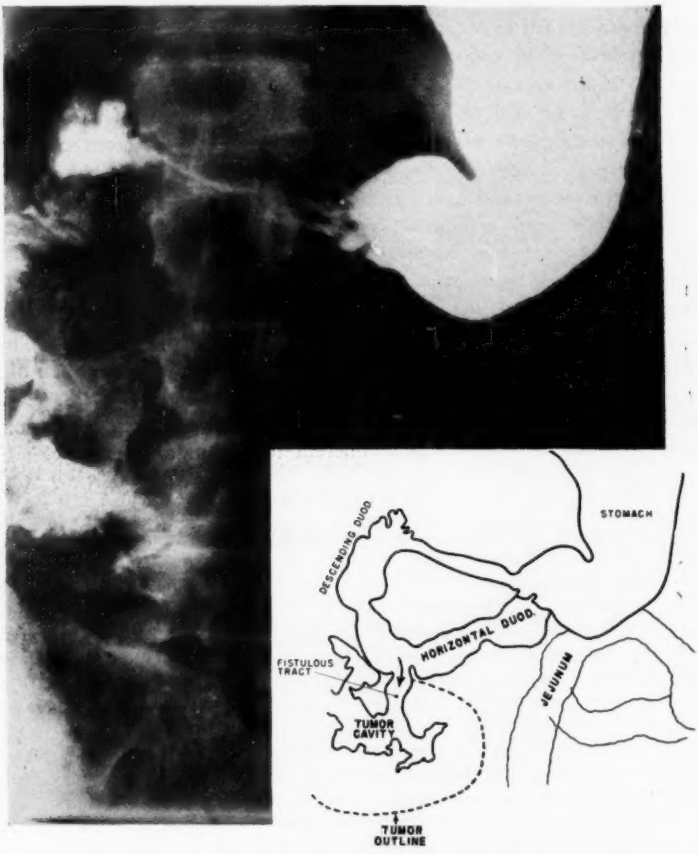

Fig. 1.—Roentgenogram showing barium of duodenum continuous with necrotic cavity in tumor. Insert is tracing of roentgenogram.

in diameter. The tumor lay within the mesenteries of the transverse colon and the mesentery of the small bowel. A careful search for metastases in the liver, mesenteries, and remaining intestinal tract and stomach revealed nothing abnormal. While freeing the tumor, it was evident that the right colic, middle colic, and ileocolic arteries would have to be sacrified together with the intestine which they supplied, since these vessels were too closely attached to the tumor mass to be separated without danger. A block dissection was then accomplished at a distance from the tumor, with the removal of the local area of duodenum, 3 ft. of terminal ileum, appendix, cecum, ascending colon, and right transverse colon. The duodenum was reconstructed

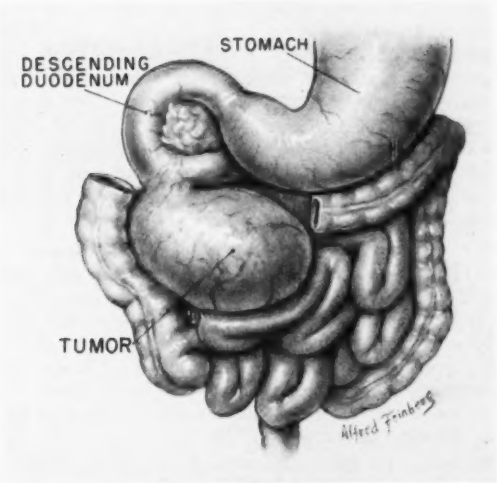

Fig. 2.—Tumor was attached to junction of descending and transverse duodenum and was size of fetal head.

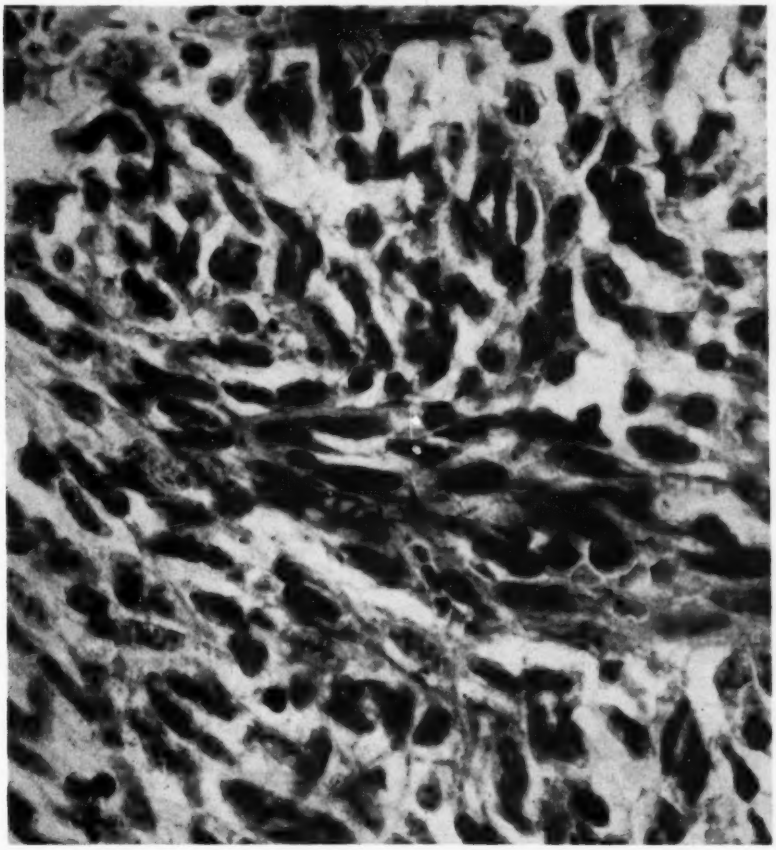

Fig. 3.—Photomicrograph (× 840). Tumor cells found replacing muscle layer consist of spindle cells with large nuclei.

by an end-to-end anastomosis, using chromic absorbable surgical (gut) suture material for the inner hemostatic layer, and interrupted nonabsorbable surgical (silk) sutures for the outer layer. The open sectioned ileum and transverse colon were then closed, and a side-to-side ileotransverse colostomy was made, using interrupted silk sutures for the outer layer and continuous chromic gut for the inner layer. The mesentery was repaired and the abdomen closed with through-and-through far-and-near wire sutures. Clips were used for the skin. The patient experienced an uneventful postoperative course while in the hospital and was discharged 10 days later, on March 24, 1952.

Pathological Report.—"Gross Description: One specimen consists of a large roughly globular mass with a portion of small intestine attached. The entire specimen measures 150 by 130 by 160 mm. On opening the small intestine (duodenum) and on transection of the tumor mass, the tumor is found to have ulcerated through the mucosa over an area roughly 3 cm. in diamter. The tumor consists of soft gray encephaloid-appearing tissue with central necrosis and hemorrhage. It is covered by peritoneum on the periphery. There is approximately 120 cm. of ileum, and the cecum and ascending colon measure 15 cm. in length. There is hemorrhage and thickening in the mesentery of the ileum, apparently the result of adhesions. On opening this portion of bowel there are no changes.

"Microscopic Description: The tumor cells found replacing the muscle layer consist of spindle cells with large nuclei. These cells are arranged in bundles. Many of the nuclei are elongated; mitoses are fairly frequent. In the ulcerated area the mucosa has undergone atrophy and necrosis."

Microscopic Diagnosis: The diagnosis was leiomyosarcoma.

Postoperative Course.—The patient was last seen on Aug. 9, 1952, five months after operation, and reported that he had been feeling well and steadily gaining weight. He was having two stools daily and would have many loose stools only with dietary indiscretions. The blood count was as follows: hemoglobin 14.2 gm. per 100 cc., red cell count 5,170,000, and white cell count 6,600, with a normal differential distribution. Urinalysis was essentially negative. In other words, he seemed to be reacting postoperatively in a way similar to any other patient who had the terminal ileum and right colon removed. At examination one year after operation, March 7, 1953, his condition was unchanged from that noted on his previous visit.

SUMMARY OF THE LITERATURE

CASE 1.—The first case of leiomyosarcoma of the duodenum was reported by von Salis [1] in 1920. He described a 40-year-old man operated on in 1918, who had been ill for seven years with recurring bouts of fever and an abdominal mass. Three operations were performed to remove the mass, and after each procedure, there was profuse drainage. Subsequently a duodenal fistula developed. This fistula was shown by x-ray to open into many cavities, as well as into the small bowel and the duodenum. At the final operation, a lobulated encapsulated tumor the size of a fetal head was found involving the fourth portion of the duodenum. Subsequently an abscess in the liver developed. At autopsy four months later, the tumor was found to be a leiomyosarcoma, not obstructing the duodenum.

CASE 2.—This case was reported by Brdiczka [2] in 1931. A 60-year-old anemic woman gave a two-week history of pain, weakness, and a palpable movable mass in the abdomen the size of a child's head. Roentgenograms demonstrated an irregularly distended duodenal bulb simulating a diverticulum and displacing the stomach and small intestine. Laparotomy revealed a leiomyosarcoma the size of a child's head. This was resected with a small piece of the first portion of the duodenum. The patient died of pulmonary embolism one week postoperatively.

CASE 3.—Andersen and Doob [3] reported on a 37-year-old machinist who had been treated for five years for a duodenal ulcer. For about seven weeks before admission he complained of an abdominal mass, weakness, tarry stools, and weight loss. The patient died of pulmonary

2. Brdiczka, I. G.: Die Tumoren der Bulbus duodeni und ihre röntgenologische Diagnose, Röntgenpraxis **3**:625-629 (July 15) 1931.

3. Andersen, D. H., and Doob, E. F.: Leiomyosarcoma of the Duodenum, Arch. Path. **16**:795-802 (Dec.) 1933.

A Tabulated Summary of All Duodenal Leiomyosarcoma Cases Reported in the Literature

Case No.	Year	Author	Age, Yr.	Sex	Duration	Pain	Weakness	Weight Loss	Anemia	Mass	Part of Duodenum	Size	Operation	Result
1	1920	Von Salis	40	M	7 yr.	....	....	....	....	Yes	4	Fetal head	Laparotomy	Death
2	1931	Brdiczka	60	F	2 wk.	Yes	Yes	....	Yes	Yes	1	Fetal head	Resection	Death
3	1933	Andersen and co-workers	37	M	5 yr.	....	Yes	Yes	Yes	Yes	3	15 cm	.....	Death
4	1934	Silverstone	51	F	2 yr.	Yes	Yes	Yes	None	Yes	3	.....	Resection	Death
5	1935	Stommel	39	M	5 wk.	Yes	Yes	Yes	None	Yes	2	Fist	Laparotomy	Death
6	1936	Seymour and co-workers	54	M	3 mo.	Yes	....	Yes	....	Yes	1	.....	.....	Death
7	1937	Nickerson and co-workers	65	M	2 yr.	Yes	Yes	Yes	....	....	2	15 cm.	.....	Death
8	1937	Nickerson and co-workers	70	F	2 mo.	Yes	Yes	....	....	....	2	.....	.....	Death
9	1938	Mendillo and co-workers	49	M	3 yr.	Yes	Yes	Yes	Yes	None	2	10 cm.	Resection	Well
10	1939	Foshee and co-workers	63	M	3 mo.	....	Yes	Yes	None	Yes	3	10 cm.	Resection	Death
11	1940	Harrington and co-workers	38	F	8 mo.	None	Yes	....	Yes	None	3	4 cm.	Resection	Well
12	1940	Mayo	..	..	.....	....	....	....	....	....	..	.....	.....	.....
13	1940	Itikawa	42	M	13 yr.	Yes	Yes	Yes	Yes	Yes	1	Fist	Laparotomy	.....
14	1941	Henning and co-workers	65	F	3 mo.	None	Yes	Yes	Yes	Yes	3	8 cm.	Resection	Death
15	1942	Shackelford and co-workers	61	F	3 mo.	....	Yes	....	Yes	....	2	8 cm.	Resection	Death
16	1944	McCullough	42	F	.....	Yes	Yes	Yes	Yes	Yes	3	8 cm.	Laparotomy	Death
17	1944	Williams	30	F	Days	Yes	Yes	....	Yes	....	4	4 cm.	Laparotomy	Death
18	1946	Brunschwig	45	M	1 mo.	....	....	....	Yes	....	3	11 cm.	Resection	Well
19	1947	Nitshe	64	F	6 mo.	....	....	....	....	....	2	2 cm.	.....	Death
20	1948	McLean	50	M	4 mo.	None	Yes	Yes	....	....	1, ?	Lemon	Resection	Death
21	1950	Heymann and co-workers	42	F	2 yr.	None	Yes	Yes	Yes	Yes	2	5 cm.	Resection	Death
22	1951	Schwartz and co-workers	55	F	.....	....	Yes	....	Yes	....	2	7 cm.	Resection	Well
23	1951	Swartz and co-workers	56	M	5 mo.	....	Yes	Yes	Yes	....	2	2.5 cm.	Resection	Well
24	1952	Ripstein and co-workers	44	M	.....	....	....	....	Yes	....	2	2 cm.	Resection	Death
25	1952	Ripstein and co-workers	53	F	3 yr.	Yes	Yes	....	....	Yes	3	.....	Resection	Death
26	1952	Ripstein and co-workers	45	M	5 mo.	Yes	Yes	Yes	Yes	Yes	1, 2	15 cm.	Resection	Death
27	1952	Ayers and co-workers	80	F	3 yr.	....	Yes	Yes	Yes	....	2	3 cm.	Resection	Well
28	1952	Weinstein and Roberts	54	M	3 mo.	Yes	Yes	Yes	Yes	Yes	3	20 cm.	Resection	Well

embolism originating in the iliac and femoral veins. At autopsy he was found to have liver metastases from a tumor 15 by 18 by 12 cm., involving the second and third portions of the duodenum. There were two areas of ulceration in the duodenum, one 3 cm. in diameter at the level of the papilla of Vater and another about 7 cm. below this area. Within the mass there was central necrosis and degeneration, with a cavity 13 cm. in depth.

CASE 4.—Silverstone [4] reported on a 51-year-old woman who complained of epigastric pain, vomiting, and weight loss. X-rays revealed nothing abnormal, but there was a palpable mass in the upper right portion of the abdomen. She also had a toxic adenoma of the thyroid, and at laparotomy a leiomyosarcoma was found arising from the third portion of the duodenum. A resection was done, as well as a posterior gastroenterostomy. She died of thyrotoxicosis on the fourth postoperative day.

CASE 5.—Stommel [5] in 1935 reported on a 39-year-old man who was operated on September, 1931, after giving a five-week history of fullness, pain in the upper abdomen of two weeks' duration, jaundice, weakness, weight loss, and a palpable mass in the upper abdomen. Roentgenograms showed no abnormalities. At laparotomy a biopsy of a firm tumor adherent to all structures, including the portal vessels, showed a leiomyosarcoma. There were liver metastases, and after an attempt at choledochostomy and gastroenterostomy, the patient died.

CASE 6.—Seymour and Gould [6] reported on a 54-year-old man with pain in the abdomen, weight loss, progressive jaundice, and a palpable abdominal mass of three months' duration. Roentgenograms revealed a filling defect of the first portion of the duodenum. At postmortem examination there was a mass 4 cm. in diameter, with ulceration into the duodenum, central necrosis, fistula formation, and abscesses compressing the common duct. A diagnosis of leiomyosarcoma of the duodenum, without metastases, was made.

CASES 7 and 8.—Nickerson and Williams [7] reported two cases of leiomyosarcoma. In the first case the patient was a 65-year-old man with a two-year history of weakness and generalized abdominal pain. Diarrhea was present for four months. The patient had lost 15 lb. (6.8 kg.) in weight. There was a cystic tumor 15 cm. in diameter near the head of the pancreas, with central necrosis and erosion into the wall of the second portion of the duodenum. In the second case the patient was a 70-year-old woman who complained of weakness and of generalized abdominal pain of seven months' duration which had become severer within the previous three days. She had a rapidly growing leiomyosarcoma of the second portion of the duodenum. This was a hard polypoid mass with many eroded parts near the surface.

CASE 9.—Mendillo and Koufman [8] reported the case of a 49-year-old white man admitted to the hospital on Oct. 11, 1937, complaining of epigastric distress of three years' duration, tarry stools, fatigue, and anemia, but no palpable mass. Roentgenograms showed a duodenal diverticulum. At operation a mass 10 by 7 by 4 cm. was resected, adherent to and involving the second portion of the duodenum. The diagnosis was leiomyosarcoma. An eight-month follow-up report stated that the patient was doing well.

CASE 10.—This case, reported by Foshee and McBride,[9] was that of a 63-year-old white man with a three-month history of weakness, a mass in the abdomen, and a 30 lb. (13.6 kg.) weight loss. A tumor the size of a fetal head was found involving the third portion of the duodenum

4. Silverstone, M.: Sarcoma of the Duodenum: Report of a Case, Brit. J. Surg. **22**:332-336 (Oct.) 1934.

5. Stommel, H. G.: Ein Fall von Leiomyosarcoma duodeni mit Lebermetastasen, Thesis, Bonn, Bonn University, 1935.

6. Seymour, W. J., and Gould, S. E.: Leiomyosarcoma of the Duodenum: Report of a Case, Am. J. Cancer **28**:572-578 (Nov.) 1936.

7. Nickerson, D. A., and Williams, R. H.: Malignant Tumors of the Small Intestine, Am. J. Path. **13**:53-64 (Jan.) 1937.

8. Mendillo, A., and Koufman, W. B.: Diverticulum and Sarcoma of the Duodenum: Report of a Case, New England J. Med. **219**:432-433 (Sept. 22) 1938.

9. Foshee, J. C., and McBride, W. P. L.: Leiomyosarcoma of the Duodenum: Report of a Case and Review of the Literature, J. A. M. A. **112**:2497-2500 (June 17) 1939.

and encroaching upon the transverse mesocolon. This was excised with a cuff of the wall, and a duodenojejunostomy was done. The tumor measured 10 by 6 by 6 cm. On the eighth postoperative day a duodenal fistula developed, and the postoperative course was steadily downward. The patient died on the 20th postoperative day. At autopsy the anastomosis was found to have broken down, and there was thrombosis of the vessels at the junction of the cecum and ascending colon. No metastases were noted.

CASE 11.—Harrington and Ganshorn [10] reported the case of a 38-year-old white woman with an eight-month history of weakness, anemia, and weight loss. There was blood in the stools. Roentgenograms showed a flat polypoid lesion at the junction of the second and third portions of the duodenum, with a region of depression or ulceration. At operation on Aug. 17, 1938, a hard fixed tumor was found in the third portion of the duodenum, measuring approximately 4 by 2.5 by 2.5 cm., with ulceration into the duodenum. A segmental resection was done and an end-to-end anastomosis was made. The postoperative course was uneventful.

CASE 12.—This case was reported by Mayo [11] in 1940, when he included the two cases found at the Mayo Clinic between 1907 and 1939. In that report he did not give any clinical history but included it in his summary of malignant lesions of the small bowel.

CASE 13.—Itikawa [12] reported on a 42-year-old man who was seen in 1939, with a 13-year history of chronic pain, tarry stools, and anemia. There were recurrent episodes 6 and 10 years previously. For the three years prior to operation the patient had pain in the right hypochondrium after eating, tarry stools, and a mass which gradually increased in size. The patient was pale and showed evidence of weight loss. A large, irregular, firm tumor was palpable. At laparotomy the tumor was the size of a fist and had several small egg-sized tumors adjacent to it. A retrocolic gastroenterostomy was done, and the postoperative course was uneventful.

CASE 14.—Henning and Garland,[13] in 1941, reported the case of a 65-year-old woman with weakness, anemia, weight loss, and a mass in the upper abdomen. Roentgenograms showed an oval filling defect in the third portion of the duodenum. At operation on Aug. 25, 1939, a lobulated, movable, orange-sized tumor was seen in the second and third portion of the duodenum. The common duct was isolated and ligated, and a cholecystojejunostomy and gastroenterostomy was done. The tumor measured 8 by 3 by 5 cm. The patient died two days postoperatively.

CASE 15.—Shackelford [14] reported on a 61-year-old woman complaining of weakness and diarrhea. There was a three-month history of gastrointestinal bleeding with anemia. A gastrointestinal series showed a defect of the descending portion of the duodenum. At laparotomy there was a mass the size of a lemon on the posterior wall of the descending duodenum, extending from a point about 1 cm. below the pylorus to the ampulla of Vater. The duodenum was resected together with a portion of the pancreas, and a gastroduodenostomy and cholecystogastrostomy was done. The patient died nine months later of metastases.

CASE 16.—McCullough [15] reported on a 42-year-old woman with weakness, pain, and a mass in the left upper abdominal quadrant. She had an 8-cm. leiomyosarcoma involving the third

10. Harrington, S. W., and Ganshorn, J. A.: Leiomyosarcoma of the Third Portion of the Duodenum: Report of a Case, Proc. Staff Meet., Mayo Clin. **15**:74-76 (Jan. 31) 1940.

11. Mayo, C. W.: Malignancy of the Small Intestine, West. J. Surg. **48**:403-407 (July) 1940.

12. Itikawa, H.: 3 Fälle von Leimyom des Verdauungstraktus: Leiomyasarcoma duodeni, Arch. jap. Chir. **17**:1270-1271 (Sept. 1) 1940.

13. Henning, B. H., and Garland, L. H.: Leiomyosarcoma of the Duodenum, Radiology **37**:353-357 (Sept.) 1941.

14. Shackelford, R. T.; Fisher, A. M., and Firor, W. B.: Duodenal Tumor of Unusual Character, Ann. Surg. **116**:864-873 (Dec.) 1942.

15. McCullough, K.: Leiomysarcoma of the Duodenum, New York J. Med. **44**:1248-1249 (June 1) 1944.

portion of the duodenum, with ulceration, sinus formation, and central necrosis. At autopsy, death was found to be caused by the formation of metastatic abscesses from the tumor, involving the liver, lungs, and heart muscle.

CASE 17.—Williams,[16] in 1944, reported on a 30-year-old woman who, 36 hours post partum, was admitted with vomiting, abdominal pain, anemia, fever, and signs of acute peritonitis. She was gravely ill, and laparotomy, with use of local anesthesia, was accomplished with the drainage of a large quantity of thin fecal fluid. At postmortem examination two days later a generalized peritonitis was found due to perforation and ulceration of a 4-cm. fungating leiomyosarcoma of the fourth portion of the duodenum, adherent to the transverse colon and liver.

CASE 18.—Brunschwig[17] in an article on the treatment of malignant tumors of the duodenum, reported a case of a leiomyosarcoma of the third portion of the duodenum. The patient was a 45-year-old man who had repeated massive gastrointestinal hemorrhage.[18] He had been operated upon twice before by other surgeons. Brunschwig did a radical resection and a duodenojejunostomy for a tumor 11 by 7 by 3.5 cm. The patient was reported alive and well three years postoperatively.

CASE 19.—Nitshe[19] reported on a 64-year-old woman, abdominally asymptomatic, who was found on postmortem examination to have a perforation of an ulcer, and a tumor of the ampulla of Vater. The tumor was a leiomyosarcoma 1.5 cm. in diameter, without ulceration.

CASE 20.—McLean[20] reported on a 50-year-old white man with a history of nausea, vomiting, weight loss, and jaundice. X-rays revealed nothing abnormal, and the patient was operated upon and found to have a movable mass the size of a lemon attached to the first and second portions of the duodenum, without metastases. A gastrojejunostomy, cholecystojejunostomy, and enteroanastomosis was done. At the second stage, during resection of the duodenum, adherence to the portal vein was discovered, and the patient died soon after.

CASE 21.—Heymann[21] in 1950, reported the case of a white woman, 42 years old, who had a history of epigastric pain, weakness, weight loss, tarry stools, anemia, and a palpable mass in the abdomen. X-rays revealed a ragged filling defect involving 2 in. of the descending duodenum. She was operated upon Jan. 8, 1948, and a block resection was done followed by a gastrojejunostomy, cholecystojejunostomy, and jejunojejunostomy. She did well for six months, and then there was evidence of metastases to the left lobe of the liver. The patient died May 15, 1949, with metastases. No autopsy was performed.

CASE 22.—Schwartz[22] reported on a 55-year-old white woman with weakness, anemia, diarrhea and tarry stools, who was found upon laparotomy to have a 7-cm. mass behind the second portion of the duodenum. A choledochojejunostomy with gastrojejunostomy and pancreaticojejunostomy was done. The mass was friable, necrotic, hemorrhagic, and ulcerated into the duodenal lumen for a distance of 5 cm. The mass was 5 by 7 by 10 cm. A 15-month survival

16. Williams, M. H. L.: A Case of Perforating Leiomyosarcoma of the Duodenum Associated with Parturition, M. J. Australia **31**:585-586 (June 24) 1944.

17. Brunschwig, A., and Tiholiz, I. C.: Surgical Treatment of Malignant Tumors of the Duodenum Exclusive of Those Arising from Papilla of Vater, S. Clin. North America **26**:163-175 (Feb.) 1946.

18. Brunschwig, A.: Personal communication to the authors.

19. Nitshe, G. A., Jr., and Suckle, H. M.: Leiomyosarcoma of the Ampulla of Vater Associated with a Tumor of the Eighth Nerve and Neurogenic Perforation of the Duodenum: Report of a Case and Review of the Literature, Am. J. Clin. Path. **17**:827-833 (Oct.) 1947.

20. McLean, R. B.: Malignancies of the Duodenum, South. Surgeon **14**:430-455 (July) 1948.

21. Heymann, J. A., and Clark, G. G.: Leiomyosarcoma of the Duodenum, Am. J. Surg. **80**:119-123 (July) 1950.

22. Schwartz, N. H.; Swingle, R. C., and Raymond, E. A.: Malignant Tumors of the Duodenum: Report of 2 Cases, A. M. A. Arch. Int. Med. **87**:410-417 (March) 1951.

was reported for this patient with leiomyosarcoma of the duodenum with metastases to the regional lymph nodes.

CASE 23.—Swartz and Eckman [23] reported on a 56-year-old white man, with weakness and weight loss for five months, in whom developed chills, fever, and jaundice, without gastrointestinal bleeding. X-rays showed a pressure defect with a mass protruding at the junction of the second and third portions of the duodenum. Laparotomy revealed a dilated gall bladder and common duct with a tumor 2.5 cm. in diameter, without ulceration, in the second portion of the duodenum just below the ampulla of Vater. Subtotal pancreatectomy, complete duodenectomy, and gastrojejunostomy were done. A diagnosis of leiomyosarcoma of the periampullary portion of the duodenum was made.

CASES 24, 25, and 26.—These cases were reported in February, 1952, by Ripstein and Flint.[24] Their first patient (Case 24) was a 44-year-old man admitted to the hospital on March 31, 1950, with complaints of pain in the right upper abdominal quadrant and melena for three years prior to admission. Gastrointestinal investigation revealed a normal stomach and duodenum, but a nonfunctioning gall bladder. At operation, in 1948, a gall bladder with stones was removed, but the stomach and duodenum showed some evidence of inflammatory reaction, without tumor or ulcer formation. The patient was well for two years and then began to complain of tarry stools occurring two or three times daily. Physical examination revealed only pallor and anemia (54%). At reoperation a mass was found in the second portion of the duodenum, and a radical pancreaticoduodenectomy was performed. The patient died on the table in cardiac arrest. A diagnosis of leiomyosarcoma of the second part of the duodenum was made.

Case 25 was that of 53-year-old white woman admitted August, 1949, with a three-year history of crampy lower abdominal pain. For one year prior to admission she had noted occasional tarry stools. There was a nontender mobile mass in the right lower quadrant, and the hemoglobin was 56%. At operation a tumor of the third part of the duodenum was found involving the ascending colon and the retroperitoneal tissues. A partial duodenectomy and a right hemicolectomy was performed. Postoperatively small bowel obstruction developed, necessitating a second operation. However, the obstruction was not relieved, and the patient died seven weeks after the initial operation. The pathological diagnosis was leiomyosarcoma of the duodenum.

Case 26 was that of a 45-year-old white man admitted in 1932, with a five-month history of weakness, epigastric pain, and weight loss of 18 lb. (8 kg.). Shortly before admission he noticed tarry stools. He was emaciated and pale, with a hemoglobin estimation of 65%. A palpable mass was present in the right epigastrium. At operation a tumor 15 cm. in diameter was found arising from the first and second portions of the duodenum and adherent to the posterior wall of the stomach. Gastrectomy was performed, and the patient died 14 days postoperatively of peritonitis and bronchopneumonia. The pathological diagnosis was leiomyosarcoma.

CASE 27.—Ayers and Cunningham [25] reported on an 80-year-old single woman with recurrent attacks of bleeding, weight loss, and severe anemia. Laparotomy, Jan. 5, 1951, revealed a leiomyosarcoma 3 cm. in diameter, of the medial wall of the second portion of the duodenum, without metastases. A cholecystectomy for cholelithiasis and a duodenal resection with an end-to-end anastomosis was done. Postoperatively the course was complicated by a pancreatic fistula, which subsided, and the patient was discharged on the 22d postoperative day. A nine-month follow-up with the patient apparently well, was reported. The tumor extended into all layers, with ulceration through the mucosa for a length of 1.5 cm.

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23. Swartz, W. T., and Eckman, W. G., Jr.: A Case Report of Leiomyosarcoma of the Duodenum, Surgery **29**:581-586 (April) 1951.

24. Ripstein, C. B., and Flint, G. W.: Leiomyosarcoma of the Gastrointestinal Tract, Gastroenterology **20**:315-326 (Feb.) 1952.

25. Ayers, W. B., and Cunningham, G. A.: Leiomyosarcoma of the Duodenum with Gastrointestinal Hemorrhage, Surgery **31**:922-927 (June) 1952.

SUMMARY AND CONCLUSIONS

Leiomyosarcoma of the duodenum is one of the rarest of tumors, this being the 28th such case to be reported. The patient has recovered from an operation which included excision of the tumor with involved duodenum, right colon, and terminal ileum.

A summary of the literature has been presented, which shows the commonest symptoms to be anemia, weakness, weight loss, bloody diarrhea, and an abdominal mass.

Of the 27 cases reported in the literature, only six patients were alive at the time the respective cases were reported. This high and early mortality is not due primarily to the unusually malignant nature of the tumor, since it is slow-growing. The answer may be found to be the location of the tumor in the duodenum, an anatomical region difficult to operate in and well known for its many postoperative complications. The frequent breaking down of the duodenal anastomosis and duodenal and pancreatic fistulization caused many early postoperative deaths.

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APPENDICES EPIPLOICAE: CLINICAL AND PATHOLOGICAL CONSIDERATIONS

Report of Three Cases and Statistical Analysis on One Hundred Five Cases

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APPENDICITIS epiploica should no longer be regarded as a surgical or pathological oddity. Owing to improved methods of diagnosis and to more painstaking and searching scrutiny of the viscera, as displayed at laparotomy, it can be demonstrated that appendicitis epiploica occurs more frequently than was commonly supposed.

After reviewing 105 cases from the literature, with 3 additional cases,[1] a comprehensive study of clinical entities related to appendices epiploicae has been made. Only those cases with symptoms primarily leading to surgical intervention are included in this series. Cases in which loose calcified bodies were fortuitously found in the abdominal cavity are deliberately eliminated because it is difficult to correlate the clinical findings, if any, with the pathological findings in these instances.

Although it cannot be classified with acute appendicitis as a highly treacherous disease, appendicitis epiploica has been directly responsible for fatalities and has caused severe surgical complications. In this light alone, appendicitis epiploica may well be emphasized in didactic teaching of differential diagnosis in abdominal conditions.

HISTORY

Credit for the first description of appendicitis epiploica goes to Vesalius, in 1543.[2] Littré,[3] in 1703, during the dissection of a cadaver, found a free hard oval

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1. One case report is from the records of the Halloran Veterans Administration Hospital, and two cases are from the records of Brooklyn Veterans Administration Hospital.

2. Vesalius, cited by Hunt, V. C.: Torsion of Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

3. Littré, cited by Davis, B. F.: Torsion of Omentum and Appendices Epiploicae: Report of 2 Cases, Minn. Med. **22**:151, 1939.

body 2.5 cm. long in the abdominal cavity. Similar findings were reported at later dates by Virchow,[4] Schede,[5] and Cruveilhier.[6] Evidence in support of the possible source of the foreign body is present in one case (Virchow) in which an atrophied appendix epiploica was found. Tomellini's case [7] was placed first in a review of cases of intra-abdominal torsion of appendices epiploicae. Tomellini demonstrated at necropsy an appendix epiploica with a pedicle which had undergone true torsion around its long axis. In 1905 Riedel [8] described an example of intrahernial torsion of an appendix epiploica in a left femoral hernial sac in a young woman.

CAUSATION

At Baylor University Hospital, over a 10-year period, 6 cases of appendicitis epiploica and 2,766 cases of acute appendicitis have been recorded, a ratio of 0.2%. Between 1950 and 1952 there have been encountered at Brooklyn Veterans Administration Hospital 2 cases of appendicitis, epiploica as compared with 120 cases of acute appendicitis, a ratio of 1.7%.

The disease occurs most commonly in persons between the fourth and fifth decades, showing its greatest incidence in those at 40 years of age. It is interesting to note that no case has been recorded in which the patient was younger than 19 years of age.

The sex frequency slightly favors males over females, in a ratio of 60 to 40%.

Pines and his associates [9] made an illuminating study on the anatomical considerations of the appendices epiploicae: The appendices epiploicae are small pouches of peritoneum laden with fat. Each appendage encloses small branches of arteries and veins which vascularize the corresponding segment of colon. These appendages are situated along the cecum, colon, upper part of the rectum, and occasionally, the vermiform appendix, but chiefly along the transverse and pelvic segments of the colon, where they are larger than elsewhere. The size also varies with the general state of nutrition, being largest and most conspicuous in obese persons and in those who have recently lost weight. They also bear a definite relation to the taeniae coli and are often arranged in two rows, one situated medial to the anterior taenia and the other lateral to the posterolateral taenia. They rarely appear in three rows and less often in one row. The average length is 3 cm., but they have been reported as long as 15 cm. Latimer [10] calls attention to an appendix

4. Virchow, cited by Hunt, V. C.: Torsion of Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

5. Schede, cited by Hunt, V. C.: Torsion of Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

6. Cruveilhier, cited by Hunt, V. C.: Torsion of Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

7. Tomellini, cited by Hunt, V. C.: Torsion of Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

8. Riedel, cited by Hunt, V. C.: Torsion of Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

9. Pines, B.; Rabinovitch, J., and Biller, S. B.: Primary Torsion and Infarction of the Appendices Epiploicae, Arch. Surg. **42**:775 (April) 1941.

10. Latimer, H. B., and Hinshaw, A. H.: An Appendix Epiploica Resembling a Vermiform Appendix, J. Kansas M. Soc. **48**:111 (March) 1947.

epiploica which was mistaken for a vermiform appendix in a cadaver in the anatomy room. The attachment of these appendages to the intestinal wall may be by a wide or narrow base.

Appendices epiploicae have been shown to appear as early as the fifth month of fetal life, but they maintain a rudimentary stature in children. This may account for a decreased incidence in appendicitis epiploica in children.

Pines and his associates [9] injected the blood vessels of the colon with a mixture of red lead and starch and traced the smallest branches to the intestinal wall. They found that the vessels to the large bowel divide at the mesenteric border of the colon within the peritoneal fat; then they encircle the wall of the bowel subperitoneally, giving off small branches to the wall. The main vessels continue into the fat of the appendix epiploica where they generally describe an inverted U-shaped arch from which branches run into the intestinal wall proximally and into the epiploic fat distally. The main vessel finally enters the intestinal wall adjacent to the border of the taenia. This acts as a safety mechanism of vascular redundancy and prevents compression of the vessels and obliteration of their lumina when the bowel is distended.

The physiological importance of an appendix epiploica is not clearly defined. However, it is reasonable to assume that it functions as a miniature omentum and has bacteriostatic and absorptive powers. It may also act as an external protective pad of the colon. Whether it is associated with movements and absorption of fluids of the large bowel is controversial.[11]

The pathological conditions, as encountered in 102 cases, may be divided into six categories: (1) torsion, 31.4%; (2) thrombosis and infarction, 15.6%; (3) gangrene, 19.7%; (4) acute inflammation and suppuration, 18.6%; (5) chronic inflammation (replacement by fibrous connective tissue, hyalinization, and calcareous degeneration), 13.7%, and (6) intussusception, 1.0%.

Although the actual twist is only occasionally demonstrated at surgery, it is generally accepted [12] that torsion of the pedicle is an important factor in compromising or strangulating the blood supply. The cause of torsion is unknown, but numerous possibilities can be postulated to initiate the chain of events: 1. Sudden rotation of the body or violent exertion. 2. Congenital malformation of an appendix epiploica so that the base is narrower and freer to rotate. 3. Anatomic arrangement of vessels such that the veins are longer and more tortuous and hence more likely to twist around an artery and produce venous occlusion. This process may be augmented by the physiologic splanchnic plethora with its characteristic mesenteric venous engorgement during the process of digestion; during this phase the distal dependent portion of the appendix epiploica is heavier and contains more fat and venous blood than does the proximal portion. 4. The appendix epiploica, heavy

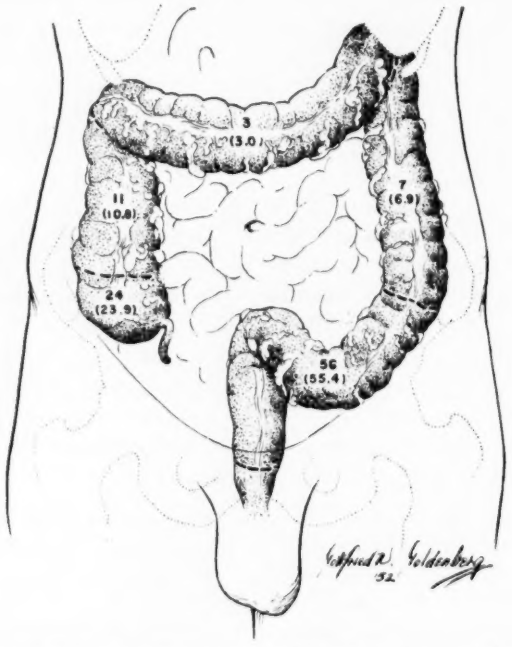
11. Robinson, R., cited by Pines.[9]

12. (*a*) Hunt, V. C.: Torsion of Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919. (*b*) Boyd, W.: Surgical Pathology, Ed. 6, Philadelphia, W. B. Saunders Company, 1947, pp. 282-283.

with fat, a likely candidate for torsion as it swings freely from the taenia. It has been noted that torsion is more likely to occur in well-nourished persons.

Torsion of an intrahernial appendix epiploica can be explained by the fact that the appendage twists on entrance into the hernial ring during a period of coughing or straining. The tip of the appendix epiploica follows along the wall of the sac, and its base or pedicle remains more or less fixed.

There are all degrees of torsion.[13] A sudden torsion is followed by subperitoneal hemorrhage, with its attendant symptoms, slight or severe, whereas an insidious twisting may be productive of chronic inflammatory changes, with its own train of symptoms resulting in ischemic fat necrosis and calcification. The necrotic mass



Anatomical location of appendicitis epiploica in 101 cases. (Number of cases are given in boldface; percentages, in parentheses.)

may be free in the abdomen or attached to the bowel wall, causing paroxysmal pain. Aseptic gangrene or primary thrombosis of an epiploic vessel is the outcome of appendiceal torsion in the absence of secondary infection. After organization of the devascularized tissue takes place, it may separate at the line of demarcation and pass off into the general peritoneal cavity as a loose body.

An explanation of primary inflammatory disease of the appendix epiploica with or without frank suppuration and in absence of torsion is offered. Lymph node

13. Upham, R., and McGrattan, V.: Torsion of Appendices Epiploicae: Review of Literature and Report of One Case, Bull. New York M. Coll. **3**:240 (Dec.) 1940.

structures within the appendix epiploica may account for it. The frequent presence of diverticula in relation to appendicitis epiploica has been noted. The relationship between diverticula and appendicitis epiploica seems to be due to the fact that these fatty masses are situated either directly on or close to points where the larger vessels enter the intestinal wall. Conceivably, bacteria may infiltrate through the wall of a diverticulum into an appendix epiploica. Not infrequently, in cases of acute diverticulitis, involvement of one or more appendix epiploica is noted, but this condition and its implications belong to the pathology of diverticulitis. This also applies to those appendices that have become secondarily infected from a vermiform appendix. A case of appendicitis epiploica occurring in conjunction with regional ileitis has been reported.[14]

Abscess formation and even general peritonitis may result either from inflammation or from torsion. More frequently, intestinal obstruction occurs in connection with inflammatory adhesive bands either between appendages or from one or another organ or from the parietes. A common cause of the obstruction is the adhesion of a pair of appendices across the antimesenteric surface of the bowel, causing narrowing of the lumen. In addition, incarceration of a cecal or sigmoidal appendix in a hernial sac may so angulate the bowel at the mouth of the sac as to give rise to actual obstruction.

From a clinical standpoint, a practical classification of abnormal epiploic appendages would segregate the intra-abdominal from the hernial appendages. To make a further breakdown into symptomatic and asymptomatic conditions, etc., as Giffin [15] does, seems superfluous from the point of view of this study. In this series, epiploic appendages were found in hernial sacs in 9 cases and in the abdominal cavity in the remaining 99 cases. The same pathological conditions prevail for both locations. However, there is an increased incidence of strangulation, rather than torsion, of the appendix epiploica in a hernial sac.

The anatomical location (Figure) of deranged appendices epiploicae, as recorded in 101 cases, is predominantly in the sigmoid colon. It is in the order of better than two to one over the other locations in the large bowel. The next most frequently encountered location is the cecum, followed by ascending colon, descending colon, and transverse colon.

The nutritional status of patients who have diseased appendages is noted and is consistent with previously obtained impressions that obesity may be a factor in the pathogenesis.[15]

SIGNS AND SYMPTOMS

Insidious in character, the signs and symptoms of diseased epiploic appendages are grossly misleading in their clinical features and, in a few instances, bizarre. They will vary considerably in individual cases and will, of course, depend somewhat on the anatomical location of the lesion. In 70% of the cases the acute symptoms lasted less than one week, in 11% there were presenting symptoms from one to

14. Massion, J.: Epiploitis During Regional Ileitis, Acta gastro-enterol. belg. **12**:715 (Dec.) 1949.

15. Giffin, H. M.; McManamy, E. P., and Waugh, J. M.: Surgical Significance of Epiploic Appendages, Arch. Surg. **45**:351 (Sept.) 1942.

four weeks, and in the remaining 19%, symptoms lasted more than one month. The mean duration of an acute episode is 18 hours. Often, mild attacks preceding the acute process may represent abortive attempts at torsion on the part of the guilty appendix. Or, in the case of a chronic appendicitis epiploica, the inflammatory process may subside in a few days, but the revived organ rarely regains its pristine state and is subject to exacerbations.

Abdominal pain is the chief complaint in every case. It may be sudden or gradual in onset and is described as dull, sharp, or colicky. The site of the pain varies with the location of the affected appendage. Pain is most frequently found in the right lower quadrant (48%), owing to the position of the sigmoid colon and cecum. Occasionally it may spread centrally, and, not infrequently, to the left side. The next commonest site is the left lower quadrant (36%).

Concomitant symptoms are nausea and vomiting in 27% and in 20% of cases, respectively. The appetite and bowels are usually unaffected, although constipation (9%) occurred twice as often as diarrhea (4.5%). The patient is usually not acutely ill. The temperature may range up to 102 F., but the average is below 99 F. orally. The pulse rate and respirations are raised only minimally. In severer cases, leucocytosis has been recorded up to 22,000, but the over-all average is 10,900 white blood cells per cubic centimeter.

Examination of the abdomen reveals signs dependent upon the site of the pathology. There is rarely generalized rigidity, but guarding of a varying degree can be detected over the affected area in 30% of the cases. Marked local tenderness is found over the affected appendix epiploica, and there may be rebound tenderness. Pines and co-workers [9] noted hyperesthesia of skin. A palpable abdominal mass was encountered in 12% of the cases; in one-third of these cases it was elicited on pelvic examination per rectum or vagina.

Appendices epiploicae undergoing torsion within a hernial sac give signs and symptoms of a strangulated hernia. Also, adhesive bands may present an intestinal obstruction.

It has recently been noted by di Rienzo [16] that appendicitis epiploica lends itself to fairly accurate roentgen diagnosis. He points out three characteristic signs on barium enema examination: (1) narrowing, completely or partially, around the circumference of the bowel, due to edema or cicatrix; (2) image of two funnels, with the apices end to end, and (3) mucosa coarsened, contracted like an accordion, and disposed perpendicular to the long axis of the colon. This is a result of extrinsic pathology. If there is a discrepancy between the x-ray signs and the palpable mass, that is, if the palpable mass is larger than the lesion as it appears on x-ray study, it is more likely to be inflammatory than malignant. Appendicitis epiploica may also be differentiated from a neoplasm pharmacodynamically by injecting 1 cc. of vasopressin (pitressin®) intramuscularly. Peristalsis is prone to stop at a neoplastic point, whereas in appendicitis epiploica the mucosal folds remain well delineated with maintenance of the stenosis as the wave passes through.

16. Di Rienzo, S., and Mosca, L. G.: El diagnostico radiologico de la epiplopericolitis, Prensa méd. argent. **36**:1306 (July) 1949.

DIFFERENTIAL DIAGNOSIS

There are no pathognomonic features of torsion of the appendix epiploica on which a diagnosis can be made preoperatively. Two cases in the entire series were diagnosed preoperatively, one by Eliason,[17] and the other by Babock, cited by Fiske.[18] In the latter case the differential diagnoses of the presenting symptoms were narrowed down considerably, since the patient had a previous appendectomy and operation for a ruptured ectopic pregnancy. In the former case, a small mass was palpated in the left lower quadrant.

Of the 108 cases analyzed, preoperative diagnoses had been made in 96. The commonest diagnosis made before operation was acute appendicitis, in 39% of cases. The differential features betwen these two entities seem more subtle than poignant. At the inception of acute vermiform appendicitis, abdominal pain is somewhat diffuse, tending to localize in the region of the epigastrium or umbilicus before shifting to the right lower quadrant some hours later. In appendicitis epiploica the pain is usually localized at the site of pathology at the onset. In vermiform appendicitis, there was habitual constipation in 60% of cases,[19] whereas in appendicitis epiploica this is a minor sign. In addition, anorexia, nausea, and vomiting are more likely to occur in cases of acute vermiform appendicitis. In general, it may be stated that patients with acute vermiform appendicitis are usually sicker. The finding of an abdominal mass in the absence of marked sepsis is more likely to be appendicitis epiploica.

Other preoperative diagnoses were subacute and chronic appendicitis 10%, diverticulitis of the sigmoid colon 9%, intestinal obstruction 6%, twisted ovarian cyst 6%, incarcerated hernia (4 inguinal and 1 femoral) 5%, acute and chronic cholecystitis 3%, tumor of the sigmoid colon 3%, and appendicitis epiploicae 2%. Torsion of an undescended testicle, sigmoiditis, abscess of the abdominal wall, cancer of the abdomen, Meckel's diverticulitis, degenerating fibromyoma, and acute surgical abdomen were each mentioned once.

COMPLICATIONS AND DEATHS

Fortunately, complications resulting from appendicitis epiploica have been minimal but, nevertheless, significant. One death [20] occurred in the present series. Three other deaths have been cited in the literature but are not well documented. All these deaths occurred before 1940.

One patient [8] died one day postoperatively of intestinal obstruction caused by a twisted appendix epiploica arising from the cecum and adherent to a portion of mesentery of small intestine. A second patient [21] died seven days postoperatively

17. Eliason, E. L., and Johnson, J.: Primary Acute Epiploitis, Surgery **6**:68 (July) 1939.

18. Fiske, F. A.: Intra-Abdominal Torsion of Appendices Epiploicae, with Report of 2 Cases and Review of Literature, Am. J. M. Sc. **192**:354 (Sept.) 1936.

19. Maingot, R.: Abdominal Operations, Ed. 2, New York, Appleton-Century-Crofts, Inc., 1948, p. 734.

20. Moore, G. A.: Appendices Epiploica, New England J. Med. **222**:919 (May 30) 1940.

21. Ebner, cited by Hunt.[12a]

of "intestinal paralysis." A third patient [22] died a few days postoperatively of general peritonitis following drainage of an abscess caused by a twisted gangrenous appendix epiploica. A fourth patient [20] died on the seventh postoperative day after pneumonia developed on the fourth postoperative day. This patient had small intestinal obstruction and strangulation resulting from the intestine wrapping itself around an appendix epiploica which had attached itself to the parietal peritoneum.

Intestinal obstruction has been a sequela of appendicitis epiploica in 9% of the cases. The small intestine is involved much more frequently than the large intestine. In one unusual case,[23] chronic partial intestinal obstruction developed from an intussusception of an appendix epiploica.

TREATMENT

The treatment of diseased appendices epiploicae is simple ligation. Although removal of an appendix may endanger the vitality of the intestinal wall, it is of little importance in those pathological conditions in which vascular damage has already taken place.

If, when an epiploic appendage is being removed, there is some possibility of an enclosed diverticulum or raw surface, the stump should be ligated and finally inverted with a Halsted mattress or purse-string suture.

Strangulated appendices epiploicae in a hernial sac should be removed and the hernia treated in a conventional manner.

The practice of testing colonic circulation after ligation of the mesocolon by removing an appendix epiploica at the appropriate level and watching for bleeding from its stump is to be discouraged.[24]

CASE 1.—A. R., a 25-year-old white man, was admitted to Halloran Veterans Administration Hospital for the fourth time, complaining of dull, crampy, abdominal pain, located primarily in the left flank and midabdomen. The patient was admitted 20, 8, and 2 months prior to the present illness with similar complaints. Thorough work-ups, including barium enema and proctoscopy, failed to sustain any diagnosis. The present illness began three days prior to admission. It did not differ from the others except for the presence of nausea and vomiting for one day at the onset and for diarrhea which persisted for three days. Physical examination revealed a blood pressure of 130/85, pulse rate of 72, and oral temperature of 98 F. A diffuse bulge of the left flank and moderate deep tenderness in the left periumbilical region were noted. No definite masses were palpable. The white blood count was 13,500, with 78% neutrophiles. The serological test for syphilis and the urinalysis revealed nothing abnormal. Stools were negative for blood, ova, and parasites. A preoperative diagnosis of acute exacerbation of a chronic appendicitis was made, although chronic diverticulitis could not be ruled out. An exploratory laparotomy was performed through a left rectus muscle-splitting incision. Acute inflammatory changes of three appendices epiploicae of the descending colon were noted. They were excised together with the vermiform appendix. The patient's postoperative course was uneventful.

The pathological report was as follows: Two irregular grey-yellow pieces of adipose tissue measured 1.5 by 1.5 by 0.5 cm. and 3.0 by 2.0 by 0.5 cm. and contained irregular bright-red foci and dilated capillaries on the external surface. Microscopic examination revealed fatty tissue

22. Seelye, W. C., in discussion on Patterson, D. C.: Appendices Epiploicae and Their Surgical Significance, with Report of 3 Cases, New England J. Med. **209**:1255 (Dec. 21) 1933.

23. Harte, M. S.: Chronic Partial Intestinal Obstruction Due to Intussusception of an Appendix Epiploica, Surgery **13**:555 (April) 1943.

24. LeVay, A. D.: Torsion and Inflammation of the Appendices Epiploicæ, Lancet **1**:141 (Feb. 1) 1941.

replaced by moderate amounts of fibrous connective tissues with hyalinization and dilated capillaries and infiltrated by diffuse collections of lymphocytes, histiocytes, plasma cells, and red blood cells. The diagnosis was chronic appendicitis epiploica.

Comment.—This case illustrates that appendicitis epiploica can recur and can remain crytogenic over long periods.

CASE 2.—C. G., a 30-year-old white man, was admitted to Brooklyn Veterans Administration Hospital, complaining of steady lower abdominal pain of three days' duration. At times the pain tended to localize in the right lower quadrant. The pain was aggravated by coughing. The patient vomited two to three times daily for three days prior to admission. He also noted urinary frequency and slight dysuria. There was an episode of diarrhea on the second day of illness. On the day prior to admission, he had anorexia, malaise, headache, and feeling of chills. The patient was a circus performer who swallowed a large number of foreign objects, including screws, bolts, and razor blades, without any deleterious effects. He also had syphilis, for which he was treated. Physical examination revealed an obese man appearing acutely ill, with a blood pressure of 124/88, pulse rate of 100, and oral temperature of 102 F. The abdomen was slightly distended. Moderate muscle rigidity was present in both lower quadrants. Direct and rebound tenderness, more pronounced on the left side, could be elicited. There was also slight tenderness in the left costovertebral angle. No masses could be palpated. Urinalysis revealed an occasional white blood cell per high power field. The white blood cell count was 14,900, with a marked shift to the left. The stools were negative for ova, parasites, and occult blood. The heterophile agglutination test showed nothing abnormal. Total protein was 6.5 gm., with an albumin-globulin ratio of 1.9. The reaction to the Kahn test was doubtful to 1+; V.D.R.L., positive, and Kolmer cardiolipin, positive. Intravenous pyelography showed no abnormalities. Because of the increasing signs of abdominal muscle spasm and tenderness laparotomy was performed for a probable appendicitis. With use of spinal anesthesia, through a left rectus muscle-splitting incision, an appendix epiploica of the sigmoid colon with intense inflammation was encountered and removed. The postoperative course was uneventful except for a superficial wound infection which responded readily to warm soaks. After recovery x-rays after a barium enema revealed diverticulosis of the sigmoid colon and numerous metallic foreign objects.

The pathology report was as follows: The specimen consisted of fat measuring 2.3 by 1.5 by 0.2 cm. The surface was dull and pink. The specimen cut with the usual consistency of fat. Microscopic examination revealed fat at the periphery. There were numerous polymorphonuclear leucocytes, lymphocytes, and plasma cells enmeshed in a partially hyalinized fibrin matrix. The diagnosis was acute appendicitis epiploica.

Comment.—The appendicitis epiploica was presumably fed by bacteria permeating the wall of a diverticulum in the sigmoid colon. That diverticulitis could not be demonstrated at laparotomy, roentgenologically or pathologically is noteworthy.

CASE 3.—C. G., a 59-year-old white man, was admitted to Brooklyn Veterans Administration Hospital complaining of sharp pains in the right lower quadrant 24 hours prior to admission. There was no anorexia, nausea, or vomiting, and no change of bowel habits. Physical examination revealed a well-developed obese white man, with blood pressure of 160/98, pulse rate 100, and temperature 99.6 F. orally. Direct and rebound tenderness was elicited deep in the right lower quadrant. No masses or organs were palpable. A left inguinal hernia was easily reducible. On rectal examination a moderate enlargement of the right lobe of the prostate was revealed. The white blood cell count was 19,200, with 80% neutrophiles. The hemoglobin content was 15.5 gm. per 100 cc. Urinalysis showed nothing abnormal. The serological test for syphilis was negative. The preoperative diagnosis was acute appendicitis. With use of spinal anesthesia, and through a McBurney incision, an appendicitis epiploica of the cecum and a normal retrocecal vermiform appendix were excised. The postoperative course was uneventful.

The pathology report was as follows: The specimen consisted of a nodular piece of fatty tissue measuring 1.5 by 1.0 by 1.0 cm. The surface contained small irregular red foci. The specimen cut with usual ease. Microscopic examination revealed large areas of hemorrhage in

fat. Within one of these areas there were collections of neutrophiles, lymphocytes, and histiocytes. The serosal surface was covered by fibrin, lymphocytes, histiocytes, and occasional polymorphonuclear leucocytes. The vermiform appendix showed fibrosis with obliteration of the lumen. The diagnosis was acute appendicitis epiploica with early infarction.

Comment.—This case is fairly characteristic of the disease.

SUMMARY AND CONCLUSIONS

One hundred five cases of appendicitis epiploica have been gathered from the literature since 1919, and 3 have been added, making a total of 108 cases.

The pathogenesis, signs, symptoms, and differential diagnosis of appendicitis epiploica are discussed.

Several fatalities and severe surgical complications have resulted from appendicitis epiploica.

The disease entity simulates acute and chronic appendicitis, and a preoperative diagnosis should be made only tentatively. Should the gross appearance of a vermiform appendix during laparotomy not account for a patient's symptomatology, it is suggested that an appendicitis epiploica be sought for. The treatment of appendicitis epiploica is surgical.

DIVERTICULITIS OF THE ASCENDING COLON

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THERE has been increasing interest in cecal diverticulitis since the first case was reported by Portier [1] in 1912. Since that time, however, no distinction between diverticulitis of the cecum and diverticulitis of the ascending colon has been made in the literature. In a recent paper we separated these two entities and stressed cecal diverticulitis.[2] The differences between them are sufficient to warrant this presentation. Up to the present there have been 14 reported cases of diverticulitis of the ascending colon.[3] To this number we are adding two cases. The pitfalls in the analysis of a limited number of cases are apparent.

INCIDENCE

According to some investigators,[4] the incidence of diverticula of the large bowel varies from 3.0 to 6.9%. Only 1.5 to 2.0% of these diverticula are recorded as occurring in the right half of the colon. It is difficult to state accurately the occurrence rate of diverticulosis of the ascending colon. However, it is very uncommon.

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1. Portier, F.: Diverticulite et appendicite, Bull. et. mém. Soc. anat. Paris **37**:29-31, 1912.

2. Vaughn, A. M., and Narsete, E. M.: Diverticulitis of the Cecum, A. M. A. Arch. Surg. **65**:763-769, 1952.

3. Bearse, C.: Acute Perforative Diverticulitis of the Colon in Young Persons, J. A. M. A. **113**:1720-1722, 1939. Carroll, H. B.: Solitary Diverticulitis of the Cecum and Ascending Colon, Quart. Bull. Northwestern Univ. M. School **17**:196-202, 1943. Bosworth, B. M., and Landau, F. L.: Solitary Diverticulum of the Ascending Colon: Case Diagnosed Before Operation, Surgery **29**:523-527, 1951. O'Callaghan, R.: Diverticulum of the Ascending Colon, Surg., Gynec. & Obst. **33**:679-680, 1921. McBee, P.: Acute Diverticulitis of the Right Colon, South. Med. & Surg. **102**:111-113, 1940. Stetten, De W.: Ileocecal Resection for Acute Diverticulitis of Solitary Diverticulum of the Ascending Colon, Ann. Surg. **104**:478-480, 1936 Shier, R. V. B.: Acute Diverticulitis of the Right Colon, Canad. M. A. J. **39**:264-265, 1938. Sartor, E.: Acute Diverticulitis of the Cecum and Ascending Colon, Acta chir. scandinav. **99**:485-488, 1950. Visconti, J. A.: Diverticulitis of the Ascending Colon Simulating Acute Appendicitis, Am. J. Surg. **32**:376, 1936. Shaw, R. E., and Siegler, J.: Acute Diverticulitis of the Cæcum and Ascending Colon, Lancet **1**:114-115, 1950.

4. Reid, D. R. K.: Acute Diverticulitis of the Cæcum and Ascending Colon, Brit. J. Surg. **39**:76-80, 1951. Willard, J. H., and Bockus, J. L.: Clinical and Therapeutic Status of Cases of Colonic Diverticulosis Seen in Office Practice, Am. J. Digest. Dis. **3**:580-585, 1936-1937. Rankin, F. W., and Brown, P. W.: Diverticulitis of the Colon, Surg., Gynec. & Obst. **50**:836-847, 1930.

The frequency of inflammatory changes is difficult to determine, but it is estimated from the literature that 14 to 17% of diverticula become inflamed. Surgical intervention in those that become symptomatic is rather low.

ETIOLOGIC FACTORS

The cause of diverticulitis of the ascending colon has not been accurately determined. There are many factors, each in itself not complete, but which combined have been offered as plausible explanations.

(*a*) Enterogenous cysts, which are commonest in the ileocecal region (remnants of duplications of the ascending colon are often considered to be enterogenous cysts)

(*b*) Hereditary factors, which are difficult to prove or to diagnose because of the limited number of cases

(*c*) Eversion of a weakened area of the bowel wall

(*d*) Traction on the appendices epiploicae, mesentery, or omentum by intra-abdominal adhesions

(*e*) Weakening of the bowel wall at the site of vascular entry

(*f*) Inherent weakness of bowel wall due to congenital factors, age, obesity or atrophy of fat along the penetrating vessels

(*g*) Increased intraluminal pressure

(*h*) Cathartics and purgatives

(*i*) Mucosal ulcerations

AGE AND SEX

Diverticulitis of the ascending colon, contrary to cecal diverticulitis, occurs more frequently in patients in the younger age group. The youngest patient reported was a 10-year-old boy, the oldest a 68-year-old woman. In most reports of diverticulitis of the ascending colon the ages of patients were between 10 and 39 years, whereas in cases of cecal diverticulitis the condition occurred most frequently in patients between the third and sixth decades. Diverticulitis of the large bowel is commoner in males. In cecal involvement the occurrence rate is practically equal between males and females. However, that of the ascending colon is twice as common in the female as in the male.

LOCATION

The location of diverticula of the ascending colon, which are usually solitary, is variable. The location was medial in six reported cases; lateral in six, and anterior in two. The location was not stated in the remaining case reports. It is interesting that none were located on the posterior aspect of the ascending colon. In one of the above cases, however, a medial-posterior aspect was tabulated. Perhaps the posterior attachment of this portion of the bowel is the limiting factor.

SYMPTOMS AND DIAGNOSIS

There is no syndrome diagnostic of acute diverticulitis of the ascending colon. The commonest preoperative diagnosis reported was acute appendicitis or one of its complications. However, in several cases there were enough atypical findings to suspect (although remote) diverticulitis of the ascending colon. The criteria

of differential diagnosis of diverticulitis of the ascending colon is that of right lower quadrant pain. Nevertheless, in cecal diverticulitis the symptoms and findings have a greater resemblance to acute appendicitis than in diverticulitis of the ascending colon. In our two cases, diverticulitis of the ascending colon was revealed at roentgenographic study and confirmed at surgery. The presenting symptoms and findings, however, had no relation to diverticula.

Diagnosis can usually be made preoperatively by barium enema examination. A correct diagnosis was made in 3 of the 16 reported cases, owing largely to the judicious use of this diagnostic procedure. Serial exposures would aid in demonstrating diverticula with a greater degree of accuracy. The hazards of barium enema in the suspect acute abdomen are obvious, but, in proper hands, it is a valuable diagnostic aid. Absence of a palpable mass does not appear significant in the differential diagnosis.

TREATMENT

Treatment of diverticulitis of the ascending colon is essentially surgical. Acute appendicitis or one of its complications may be difficult to rule out. Therefore exploration is indicated. In the reported cases the surgical procedure varied from simple drainage to a right colectomy. In our opinion, the most adequate conservative surgical procedure should be performed. During exploration, carcinoma may be considered. Rapid frozen section studies may be of some value in determining the presence of carcinoma. However, if there is reasonable doubt, wide resection should be done. In the reported cases resection was performed eight times, diverticulectomy four times; opening and suture of the diverticulum in two cases; marsupialization in one, and simple drainage in one. The appendix was essentially uninvolved in all cases, but incidental appendectomy was usually performed. A fecalith was present in the diverticulum in 50% of the reported cases. The literature reveals less peridiverticular reaction in diverticulitis of the ascending colon than in cecal diverticulitis.

COMPLICATIONS

There has been no mortality of diverticulitis of the ascending colon reported in the literature. Complications were encountered in four cases (25%). Postoperative distention was present in two cases, a fecal fistula in one, and a subcutaneous abscess in another. It can even be said that the morbidity of this entity is equal to that of cecal diverticulitis, but the mortality of cecal diverticulitis is greater.

REPORT OF CASES

CASE 1.—G. C., a white man aged 50, was admitted to Mercy Hospital, Loyola University Clinics, in April, 1947, complaining of diarrhea and melena. He had been well until two months prior to admission when he had diarrhea and melena for four days. He had had a similar episode one week previously and noted bright red blood from the rectum. Hemorrhoids had been present for some time.

Physical examination revealed a well-developed, obese white man, not acutely ill. A fine apical systolic-diastolic murmur was audible throughout the precordium and transmitted to the left axilla. The abdomen was essentially normal, except for a questionable mass in the right lower quadrant. Rectal digital examination revealed no abnormalities. Barium enema examination demonstrated a solitary diverticulum on the lateral aspect of the upper third of the ascending colon. However, carcinoma of the ascending colon could not be ruled out. The patient was prepared for surgery.

The abdomen was entered through a right transrectus incision. There was a mass about 5 cm. in diameter on the lateral aspect of the ascending colon approximately 3 in. (7.6 cm.) above the ileocecal valve. The neck of the diverticulum was filled with barium which was dislodged in mobilizing the ascending colon. An opening was felt from the diverticulum into the ascending colon, large enough to admit the tip of the index finger. The appendix was large but appeared normal. Exploration revealed no other significant pathology. A wedge was taken from a representative area for frozen section studies. The pathologist reported no evidence of tumor cells. Therefore the diverticulum was split and sutured. Incidental appendectomy was not performed, since further surgery was deemed inadvisable. A cigarette drain was inserted and the layers of the abdomen repaired routinely. The postoperative course was stormy, as decompensation and abdominal distention developed. He responded well to therapy, but there was drainage from the wound. He was ultimately discharged in good condition. A roentgenogram, taken six years later, showed a normal bowel pattern, and the patient has been asymptomatic.

Case 2.—E. R., a woman aged 67, was admitted to Mercy Hospital, Loyola University Clinics, in March, 1951, complaining of left subcostal pain. She had been apparently well until two years prior to admission, when she experienced sharp left subcostal pain, which was relieved by the application of heat. This pain occurred at infrequent intervals since its initial onset. One year later arthritis developed in the right knee but responded to therapy. Pain in the left subcostal area migrated to the left lower quadrant and became sharper. The patient's appetite became poor. Melena was observed two weeks before admission. The patient had received radium therapy for postmenopausal bleeding.

Physical examination revealed a well-nourished, thin white woman, not acutely ill. There was a soft nodule along the lateral aspect of the right shoulder. The heart and lungs were essentially within normal limits. The abdomen was normal except for moderate tenderness in the left lower quadrant. No masses were palpated. There were mild to moderate varicosities of the left saphenous vein.

The urine and blood counts were normal. Occult blood was present in the stool. Nonprotein nitrogen, fasting blood sugar, and serum proteins were within normal ranges; serum albumin was 4.0 and serum globulin 4.70 mg. per 100 cc. A barium enema examination demonstrated a solitary diverticulum on the medial aspect of the ascending colon just above the cecum. An upper gastrointestinal roentgenogram series demonstrated no pathology. The patient was prepared for surgery.[5]

The abdomen was entered through a right paramedian incision. A solitary diverticulum on the medial aspect of the ascending colon just above the ileocecal valve was located. Appendectomy was performed. Exploration revealed no other significant pathology. The diverticulum was therefore dissected from the surrounding structures. A clamp was applied at its base and the diverticulum removed.

Repair was by Kerr-Parker suture with a reinforcing layer of interrupted chromic (gut) absorbable surgical, sutures. The diverticulum measured 2 cm. in diameter and contained a firm fecalith. Microscopically this was a false diverticulum. The patient's postoperative course was smooth, and she was discharged on the 11th postoperative day.

COMMENT

The separation of cases of cecal diverticulitis from cases of diverticulitis of the ascending colon may appear academic, inasmuch as both are most difficult to differentiate from acute appendicitis. However, there are several essential factors which aid in differential diagnosis. Primarily, their location is different. Diverticulitis of the ascending colon produces symptoms and signs of appendiceal involvement less typical than those of cecal diverticulitis. Pathologically there is less tendency to actual involvement of the appendix in diverticulitis of the ascending colon. In addition, cecal diverticula occur with equal frequency in males and

5. Credit is given to Drs. M. W. K. Byrne and J. Scheid.

females, but diverticula in the ascending colon are commoner in females. Moderate disparity also exists in the age group, as diverticula of the cecum occur in patients in the later decades. There is also more peridiverticular reaction in cecal diverticulitis.

In our two cases the presence of melena and rectal bleeding could not necessarily be attributed to the diverticulum. This was particularly so in Case 1, as the patient had hemorrhoids. In Case 2, the right-sided diverticulum could not be incriminated for the left-sided pain, but may have caused melena. However, the patient has been asymptomatic since surgery.

SUMMARY AND CONCLUSIONS

The literature reveals only 14 cases of diverticulitis of the ascending colon. This entity is discussed and two additional cases are reported.

The cause of diverticulitis of the ascending colon has not been definitely established. The more important etiologic factors suggested in the literature have been presented and discussed.

Diverticulitis of the ascending colon may and does cause a syndrome simulating appendicitis, although there is less tendency to involvement of the appendix in diverticulitis of the ascending colon than in cecal diverticulitis.

The judicious use of barium enema examination with serial exposures is of diagnostic value.

The treatment of diverticulitis of the ascending colon is usually surgical, since acute appendicitis cannot be ruled out.

The surgical procedure varies from drainage to right hemicolectomy, depending upon the type of pathology present.

In our cases the atypical finding of melena was noted.

EFFECT OF HEPATIC ARTERY LIGATION ON ASCITES DUE TO LAENNEC CIRRHOSIS

Report of Two Cases

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IT IS GENERALLY held that the cause of portal hypertension in cases of Laennec cirrhosis is the result of diffuse fibrosis within the liver so that the intrahepatic portal veins are narrowed and compressed. Thus portal blood reaching the right heart seeks a route that bypasses the liver. One of these routes is through the coronary vein of the stomach to the veins of the esophagus and thence through the azygos system to the right side of the heart. In the esophagus the veins are poorly supported; pressure produces varices, and rupture not uncommonly results in fatal hemorrhage. Although many surgical procedures have been used in the treatment of varices of the esophagus, none has been entirely successful. Indeed, the prevention of hemorrhage from such varices remains an outstanding surgical problem.

This difficulty would be resolved if a method were found that would effect an increase in the flow of blood in the portal veins through the cirrhotic liver. There is some evidence that this may be achieved. In 1907 Herrick [1] investigated the circulation of cirrhotic livers by means of perfusion experiments. He found that with perfusion of the hepatic artery of the normal liver most of the perfusate escaped from the hepatic vein but some issued from the portal vein. Also, it was found that the pressure in the portal vein in the normal liver increased 1 mm. for each increase of 40 mm. Hg pressure in the hepatic artery. Similar perfusion of the cirrhotic liver revealed most of the perfusate leaving the liver through the portal vein, although some issued from the hepatic vein. In the cirrhotic lever the portal vein pressure increased 1 mm. for each 6-mm. increment in the pressure of the hepatic artery, so that with a hepatic artery pressure of 130 mm. Hg, the perfusate issued from the portal vein with a pressure of 20 mm. Hg. This indicated to Herrick that the perfusate passed from hepatic arterioles through anastomoses that opened into portal venules, thus transmitting systemic arterial pressure to the main portal venous channels.

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1. Herrick, F. C.: An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93, 1907.

Herrick next perfused the portal veins of normal and cirrhotic livers. He found that the volume flow through the cirrhotic livers was greater than in normal livers. He stated that the vascular capacity of the cirrhotic liver appeared to be increased, and he did not find intrahepatic obstruction of the portal vein.

The next investigation was to determine the effect of pressure in the hepatic artery on the flow of perfusate through the portal vein. Herrick detected no appreciable change in portal vein pressure in the normal liver until the hepatic artery pressure exceeded 100 mm. Hg. In the cirrotic liver, however, portal vein pressure began to rise when the hepatic artery pressure reached 30 mm. Hg. Herrick concluded that in the liver of portal cirrhosis there are far freer communications between the arterial and portal currents than in the normal liver. He believed that the transmission of hepatic artery pressure to the portal veins through dilated capillary anastomoses in the perilobular fibrous tissue was an important factor in the cause of portal hypertension in cirrhosis.

Other evidence was consistent with this concept of Herrick. In 1911 Winternitz [2] concluded from his investigations that the hepatic artery communicated with the portal vein before emptying into the hepatic sinusoids. In 1930 Cameron and Mayes [3] also believed that presinusoidal anastomoses existed, but they were unable to demonstrate these channels. In 1942, Wakim and Mann [4] investigated the intrahepatic circulation of the rat and found that most of the vascular spaces of the liver were inactive (empty) under normal conditions. After examining the small vessels, they stated that the hepatic artery delivered blood into the interlobular branches of the portal vein, as well as directly into the sinusoids. In 1942 Dock [5] conducted experiments similar to those of Herrick and concluded that in large fatty livers and in most cirrhotic livers the total hepatic perfusate was decreased and the rise in portal pressure was due chiefly to a diminished portal bed in the liver. However, in some cases, which he designated as "alcoholic," the hepatic arterial bed was distinctly increased, and he postulated that in all "alcoholic" cirrhoses the portal hypertension was more marked than it would have been if the hepatic arterial inflow were reduced. Dock stated that some damage at the arterioportal junction must be assumed to account for this change, and he added, "In healed alcoholic cirrhosis, with ascites or danger of fatal esophageal hemorrhage, a procedure to reduce the hepatic inflow may be worth consideration. . . ." Dock later stated,[6] after volume flow studies with oil, "It was our impression that portal perfusion was usually normal in cases of much perilobular scarring but with little fatty change or necrosis of the parenchyma." Further work revealed the average hepatic artery inflow in cirrhotic livers to be 1,360 cc. per minute, while in the normal liver the average was 1,100 cc. per minute. This was interpreted as confirming Herrick's

2. Winternitz, M. C.: The Effect of Occlusion of the Various Hepatic Vessels upon the Liver, Bull. Johns Hopkins Hosp. **22**:396, 1911.

3. Cameron, G. R., and Mayes, B. T.: Ligation of the Hepatic Artery, J. Path. & Bact. **33**:799, 1930.

4. Wakim, K. G., and Mann, F. C.: The Intrahepatic Circulation of Blood, Anat. Rec. **82**:233, 1942.

5. Dock, W.: The Role of Increased Hepatic Arterial Flow in Portal Hypertension of Cirrhosis, Tr. Am. Physicians **57**:305, 1942.

6. Dock, W.: Shattuck Lecture: The Clinical Significance of Some Peculiarities of the Circulation in the Kidneys, Liver, Lungs, and Heart, New England J. Med. **236**:773, 1947.

report of increased volume flow through the hepatic artery in cirrhosis. Dock stated that this was presumably due to the development of numerous intrahepatic arteriovenous fistulas analogous to angiomas present in the skin of cirrhotic patients. In 1945 Bollman [7] stated that presinusoidal channels become prominent in cirrhosis produced experimentally by carbon tetrachloride. He stated:

> Vascularization of the regenerated regions were mainly arterial, the central veins were displaced and the larger arterial and venous channels became very tortuous. There seemed to be more direct communication between branches of the hepatic artery and the portal vein and larger anastomotic channels to the hepatic veins from both the artery and the portal vein.

Clinical information indicating the presence of hepatic artery anastomoses to portal veins in cirrhotic livers was supplied by Cohn in a personal communication to Dock.[5] Cohn described four cases of advanced cirrhosis in which at laparotomy brief occlusion of the hepatic artery by digital pressure caused portal vein pressure to drop as much as 7 to 11 cm. of water. In these cases, the systemic arterial pressure did not exceed 80 mm. Hg, so that with normal systemic pressure a greater drop in portal pressure might be expected. This evidence, although fragmentary, was consistent with the concept originally advanced by Herrick, that anastomoses between hepatic arterioles and portal venules develop in the perilobular fibrous connective tissue, and that transmission of arterial pressure into the portal veins is, in part, responsible for the intrahepatic venous obstruction in cirrhosis.

A dissenting opinion to this concept was expressed by McIndoe.[8] In 1928 he attempted to duplicate the work of Herrick. However, when the portal vein was perfused, most or all of the perfusate escaped through collateral channels in the liver capsule. McIndoe stated:

> The results were so inconstant and the effect so slight as to make negative, in my own mind, at least, the possibility that the high pressure arterial stream entering the low pressure venous stream in such a condition as cirrhosis could produce enough back pressure to be the chief factor in the cause of portal hypertension in cirrhosis.

However, he did make corrosion specimens that showed gross alterations of the hepatic vessels in cirrhotic livers. Thus McIndoe did not refute the concept of Herrick; he simply was unable to duplicate the perfusion experiment.

For clinical application it was first necessary to demonstrate that hepatic artery ligation could be performed in the experimental animal without untoward effects. This was reported in 1949 by Markowitz, Rappaport, and Scott [9] and by Davis, Tanturi, and Tarkington.[10] They showed that this procedure was possible in dogs if the animals were protected from anaerobic infections by giving antibiotics during a short postoperative period. This work was also successfully carried out by Tanturi, Swigart, and Canepa [11] and by Chau, Goldbloom, and Gurd [12] in 1950.

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7. Bollman, J. L.: Conference on Liver Injury, Transactions of the 3rd Conference, 1945, New York, Josiah Macy, Jr., Foundation, 1945.

8. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, Arch. Path. **5**:23, 1928.

9. Markowitz, J.; Rappaport, A., and Scott, A. C.: Prevention of Liver Necrosis Following Ligation of Hepatic Artery, Proc. Soc. Exper. Biol. & Med. **70**:305, 1949.

10. Davis, L.; Tanturi, C., and Tarkington, J.: The Effect of Reduced Blood Flow to the Liver in Renal Hypertension, Surg., Gynec. & Obst. **89**:360, 1949.

11. Tanturi, C.; Swigart, L. L., and Canepa, J. F.: Prevention of Death from Experimental Ligation of the Liver (Hepatic Proper) Branches of the Hepatic Artery, Surg., Gynec. & Obst. **91**:680, 1950.

12. Chau, A. Y. S.; Goldbloom, V. C., and Gurd, F. N.: Clostridial Infection as a Cause of Death After Ligation of the Hepatic Artery, A. M. A. Arch. Surg. **63**:390, 1951.

Successful results of this procedure were again reported by Grindlay, Mann, and Bollman [13] in 1951.

These reports stimulated hope that the human cirrhotic liver, protected with antibiotics, would withstand hepatic artery ligation. If the concept of Herrick regarding the cause of portal hypertension in cirrhosis were correct, then clinical improvement from this procedure might be expected. In 1951 Berman, Koenig, and Saint [14] described the successful application of this procedure in a case of advanced cirrhosis with pronounced ascites. The accumulation of ascitic fluid stopped abruptly. Shortly after this, Rienhoff [15] published a preliminary report in which beneficial results were obtained in 2 cases of advanced cirrhosis, and he mentioned 10 other cases in which improvement was noted. Rienhoff and Berman separately emphasized that both the hepatic and the splenic arteries should be ligated. Later, Berman [16] published a report of an additional case and stated that the hepatic artery should be ligated close to its origin from the celiac plexus so that the liver would be nourished with oxygenated blood through collateral vessels. Recently, Berman and Hull [17] reported the treatment in 12 cases of portal cirrhosis in which they advised ligation of the left gastric artery in addition to ligation of the hepatic and splenic arteries.

Our interpretation indicated that the major arterial supply of the liver should be occluded, for only in this way could a maximum reduction of transmitted systemic pressure into the portal veins be accomplished. Therefore ligation of the left hepatic artery and right hepatic artery distal to the cystic branch or ligation of the common hepatic artery with excision of the fundus of the gall bladder was proposed. This was performed in two cases and the results are of interest.

CASE 1.—The patient was a white woman, 34 years old, who had been a chronic alcoholic for several years. Five months before admission, she was hospitalized for a period of one month and was treated with a special diet and "liver shots." At this time, swelling of the abdomen was first noted. This was progressive during the next four months, and she then entered Wesley Memorial Hospital (Nov. 9, 1951). The patient stated that she had been drinking 1 pt. to 1 qt. of whiskey daily for the past 15 years.

Past history revealed that she had pneumonia during childhood, and for the past several years there had been dyspnea and cough productive of up to two cups of thick sputum daily. Hysterectomy had been performed two years prior to admission. There had been no hematemesis, jaundice, melena, or hemoptysis.

Physical examination revealed a moderately well-nourished white woman in no distress. The temperature was 97.6 F., pulse rate 92, respiration 24, blood pressure 114/76 mm. Hg. The head and neck were normal. "Spider angiomas" were present over the skin of the arms, upper

13. Grindlay, J. H.; Mann, F. C., and Bollman, J. L.: Effect of Occlusion of the Arterial Blood Supply to the Normal Liver: An Experimental Study, A. M. A. Arch. Surg. **62**:806, 1951.

14. Berman, J. K.; Koenig, H., and Saint, W. K.: Ligation of the Hepatic and Splenic Arteries in the Treatment of Portal Hypertension, Indiana Univ. Quart. Bull. **12**:99, 1950.

15. Rienhoff, W. F., Jr.: Ligation of the Hepatic and Splenic Arteries in the Treatment of Portal Hypertension with a Report of 6 Cases: Preliminary Report, Bull. Johns Hopkins Hosp. **88**:368, 1951.

16. Berman, J. K.; Muller, L. P.; Fisch, C., and Martz, W.: Ligation of the Hepatic and Splenic Arteries in a Patient with Atrophic Cirrhosis of the Liver, A. M. A. Arch. Surg. **63**:623, 1951.

17. Berman, J. K., and Hull, J. E.: Hepatic, Splenic, and Left Gastric Arterial Ligations in Advanced Portal Cirrhosis, A. M. A. Arch. Surg. **65**:37, 1952.

part of the chest, and back. There was no cardiac murmur and the heart was not enlarged. Rales were heard throughout both lungs. The abdomen was distended and soft, and a fluid wave was elicited (Fig. 1). Tortuous blue veins were present over the abdomen and chest. The extremities were normal, and the remainder of the physical examination was unremarkable.

The uncatheterized urine was not remarkable except for 15 to 20 leucocytes per high power field. Other laboratory data are listed in Table 1. The reaction to the Kahn serologic

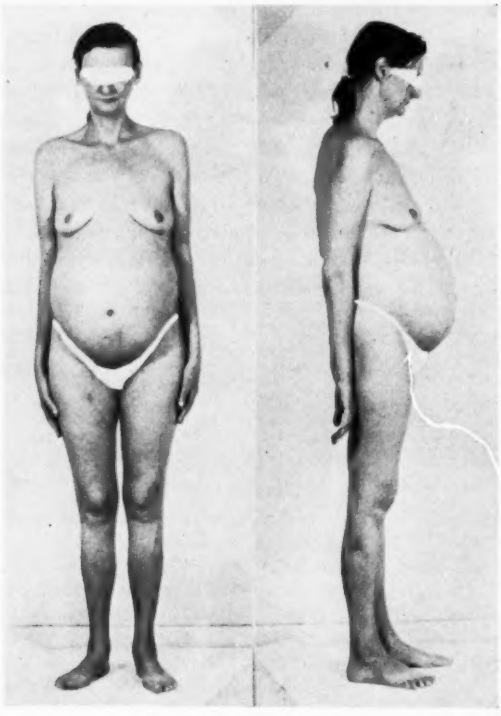

Fig. 1 (Case 1).—Patient nine days before hepatic artery ligation.

TABLE 1.—*Laboratory Data of Case 1**

Hospital Day †	2	16	28	31	37	42	76
Hemoglobin, gm./100 cc.	10.1	...	...	....	10.5	...	13.5
Erythrocytes	3,390,000	...	...	....	3,460,000	...	4,630,000
Leucocytes	8,800	...	...	....	22,700	...	27,600
Icterus index	6.3	...	6.4	12.7	....	8.3	4.2
Total protein, gm./100 cc.	5.67	...	6.35	7.25	7.25	6.53	6.89
Albumin, gm./100 cc.	2.64	...	3.00	3.06	3.48	3.12	3.66
Globulin, gm./100 cc.	3.03	...	3.35	3.47	3.77	3.41	3.23
Thymol turbidity, units	2	...	3	3	3	4	4
Cephalin flocculation ‡	....	1+	4+	2+	3+	1+	1+
Nonprotein nitrogen, mg./100 cc.	20.0	...	20.5	....	20.0	...	....
Alkaline phosphatase, Bodansky units	2.4	...	2.8	4.2	17.6	11.4	5.1
Weight, lb.	155	139	...	....	120	119	119

* Hepatic artery ligation was performed on the 27th hospital day.
† Hospital days are counted from initial day of admission.
‡ Cephalin flocculation is expressed in 48 hour values.

test was negative. Barium studies of the esophagus and upper and lower gastrointestinal tract showed no abnormalities. X-rays of the chest revealed linear fibrosis at the base of the left lung, and the fields were otherwise clear.

On the first hospital day, paracentesis yielded 9,800 cc. of clear pale-yellow fluid. Beginning on the seventh hospital day, intramuscular injection of meralluride (mercuhydrin®) sodium, 2 cc., was given on alternate days for six doses, after which it was permanently discontinued. Salt was at no time excluded from the diet. During the nine-day period after use of meralluride sodium was discontinued and before operation, there was a weight gain of 4 lb. (1.8 kg.).

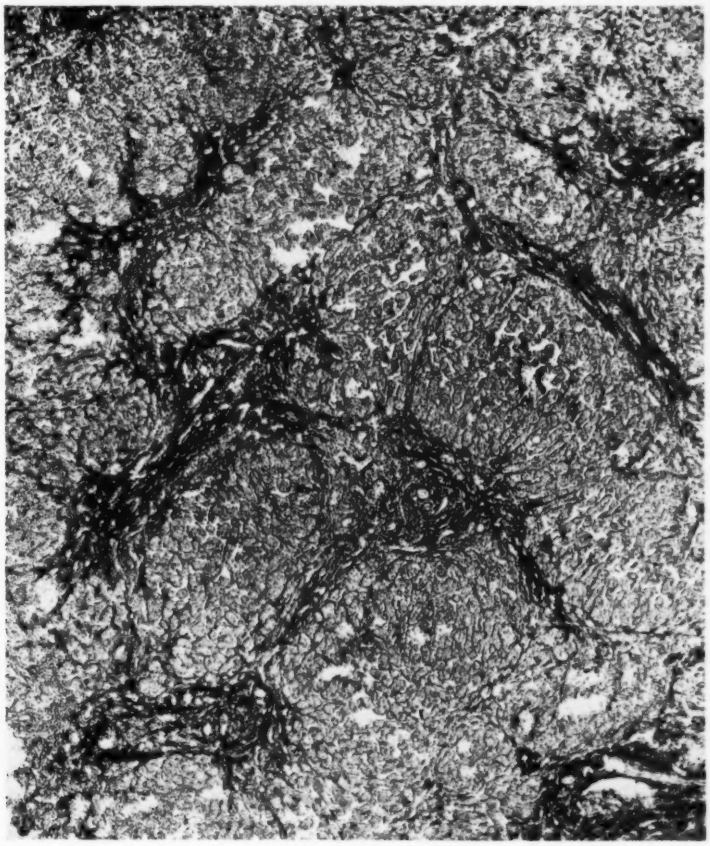

Fig. 2 (Case 1).—Photomicrograph of liver section, showing Laennec cirrhosis; trichrome stain.

One cubic centimeter of "combiotic" [18] twice daily was given on the seventh hospital day and was continued for 13 days. Its use was then discontinued and resumed two days before operation and was maintained until the 45th hospital day. In addition, terramycin, 500 mg. four times daily, was given from the 35th to the 43rd hospital day.

On the 27th hospital day (Dec. 4), the patient was anesthetized with ether and cyclopropane, and the abdomen was entered through an upper midline incision. The peritoneal space was

18. Penicillin, 400,000 units, and streptomycin, 1 gm., per cubic centimeter.

emptied of 7,800 cc. of clear pale-yellow transudate. The liver was firm, dark red, and finely nodular. The mesenteric veins were dilated. A needle connected to a water manometer was inserted into the portal vein, and the pressure was 31 cm. After digital occlusion of the hepatic artery, the pressure fell to 29.5 cm. of water. The hepatic artery was doubly ligated distal to the superior gastroduodenal branch. A biopsy specimen of the liver was taken, and histologic examination revealed Laennec cirrhosis (Fig. 2). The abdomen was closed, and the patient was returned to her room in good condition.

During the postoperative period, there were fever and right upper quadrant abdominal pain, and the latter was increased by deep inspiration. The latter was attributed to fibrinous adhesions about the porta hepatis, and this pain gradually subsided. A temperature of 103.4 F. was reached

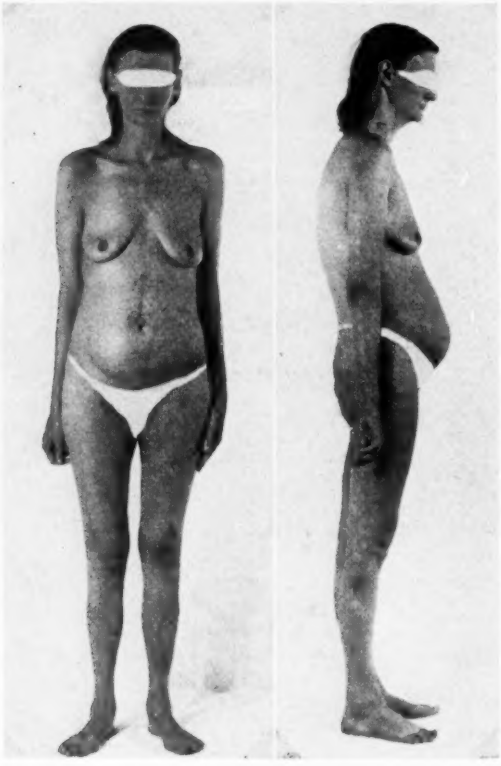

Fig. 3 (Case 1).—Patient 122 days after hepatic artery ligation.

on the sixth postoperative day, but this returned to normal four days later. Sulfobromophthalein retention before operation on the 10th hospital day was 20%, on the 48th hospital day 6%, and on the 76th hospital day 4%. The first two determinations were made 45 minutes after injection of the dye, and the last 50 minutes afterward. Prothrombin time on admission was 33% of normal. After vitamin K was given this value rose to 88%, and on the first postoperative day was 60%. Evidence of a bleeding tendency has not been detected since operation. It was believed that a reduction of portal vein pressure by hepatic artery ligation would be manifest by a decrease in the dilated veins over the chest and abdomen. This change was

observed clinically. During the latter part of the hospital course, the patient felt well, and strength and sense of well-being improved. There was no recurrence of ascites, and she was discharged after 47 days in the hospital (Dec. 26).

One month later the patient returned with the complaint of perirectal pain, and examination revealed bilateral ischiorectal abscesses. These were opened and drained. She stated that during the month at home she felt better than at any time for the past several years and that she had a hearty appetite and ate without restriction. Laboratory tests performed at this time are listed in the right-hand column of Table 1 under 76th hospital day. The patient returned home after seven days. Since the operation, she has felt well and her appetite has been good. However,

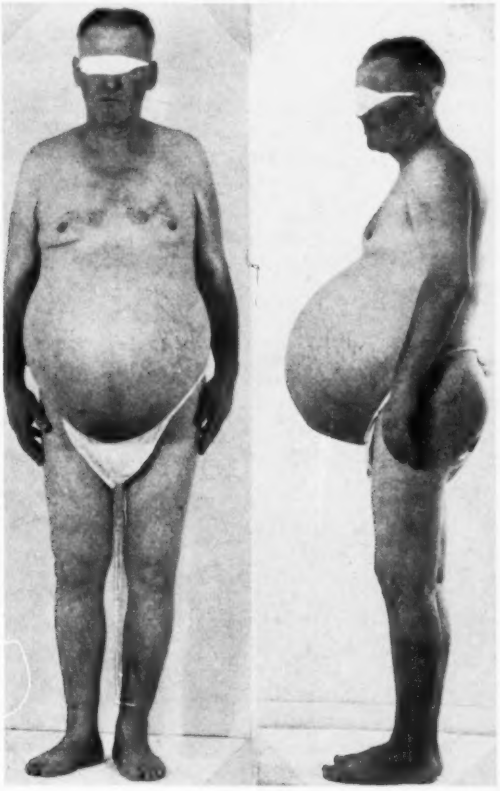

Fig. 4 (Case 2).—Patient eight days before hepatic artery ligation.

during the six months after operation (May 4, 1952), there has been slight abdominal enlargement, although paracentesis has not been necessary. It is believed that this may be due to a nonligated accessory hepatic artery which, according to Lander, Lyman and Anson,[19] is not uncommon.

Comment.—The patient withstood the procedure of hepatic artery ligation well and there was benefit, as judged by clinical appearance and by her subjective sensa-

19. Lander, H. H.; Lyman, R. Y., and Anson, B. J.: An Anatomical Consideration of the Structures in the Hepatic Pedicle, Study of 100 Consecutive Cadavers, Quart. Bull. Northwestern Univ. M. School **15**:103, 1941.

tions. Laboratory data before operation revealed only a slight anemia, slight hypoproteinemia, and reversal of the albumin and globulin fractions. In addition, the thymol turbidity was 2 units. After operation, there was a slight and transient rise of the icterus index and a return of the total plasma proteins to normal. Both protein fractions increased, so that at the last determination, albumin was in slight excess of globulin. The erythrocyte count rose. Cephalin flocculation and alkaline phosphatase both revealed a transient increase after operation, with return to normal. Only thymol turbidity remained elevated after operation.[20] The appearance of the patient 122 days after hepatic artery ligation is shown in Figure 3.

CASE 2.—The patient was a 45-year-old white man, a bartender, who was well until 11 months prior to hospital admission. At that time (Nov. 26, 1950) he noted slight edema of the lower legs and feet. About one week later, he became aware of gradually progressing abdominal enlargement. He sought medical care and was given intramuscular injections, after which the peripheral edema subsided, but the abdominal swelling persisted. Two months after the onset, the abdomen was so large that a paracentesis was performed, and 3 to 4 gal. (12 to 16 liters) of fluid was removed. One month later a second paracentesis yielded 3 to 4 gal. of

TABLE 2.—*Laboratory Data of Case 2**

Hospital Day †	2	5	11	13	17	40	44
Hemoglobin, gm./100 cc.	15.1	....	....	....	14.4	....	....
Erythrocytes	5,120,000	....	....	....	4,600,000	....	....
Leucocytes	12,300	....	....	....	....	....	....
Icterus index	7.6	7.3	16	16.2	12.2	6.9	....
Total protein, gm./100 cc.	6.93	5.84	5.74	6.01	6.23	6.71	6.53
Albumin, gm./100 cc.	3.48	3.00	2.88	2.88	2.88	3.54	3.60
Globulin, gm./100 cc.	2.91	2.84	2.87	3.13	3.35	3.17	2.93
Thymol turbidity, units	2	....	1	1	1	1	....
Cephalin flocculation	Normal	Normal	....	....	Normal	....	....
Prothrombin time ‡	79	....	....	87	83	....	....
Sulfobromophthalein §	20	....	....	....	28	....	....
Nonprotein nitrogen, mg./100 cc.	23.7	25.0	29.5	25.4	23.7	25.8	29.0
Alkaline phosphatase, Bodansky units	....	21.3	....	....	17.5	25.6	20.2

* Hepatic artery ligation was performed on the ninth hospital day.
† Hospital days are counted from initial day of admission.
‡ Prothrombin time is expressed in per cent of normal.
§ Sulfobromophthalein is expressed in per cent retained per 100 cc. in 45 minutes.

ascitic fluid. During this illness of 11 months, there were 10 paracenteses. Each of the last five yielded fluid in excess of 5 gal. (20 liters) and the last yielded 7 gal. (28 liters). The average interval between paracenteses was six weeks. The rate of weight gain during this period was approximately 1½ lb (0.7 kg.) daily. It is estimated that the patient was accumulating ascitic fluid at the rate of 16,000 cc. every 30 days.

The patient stated that he had been a "chronic alcoholic" for the past 20 years, ingesting over 1 qt. of whiskey daily for the past 6 years. There had been no jaundice, hematemesis, melena, or hemoptysis.

Physical examination revealed a well-developed, moderately well-nourished white man in no distress. The temperature was 99.2 F., pulse rate 72, respirations 28, blood pressure 120/80 mm. Hg. "Spider angiomas" were present over the malar eminences and over the neck, shoulders, upper portion of the chest, and back. There was slight wasting of the shoulder girdle muscles. The heart and lungs were normal. The abdomen was nontender, tense, and markedly distended (Fig. 4). A fluid wave was elicited. Numerous blue venous channels were present over the chest and abdomen. The external genitalia and extremities were normal.

20. Recent information reveals that the patient has been well, except for recurrent alcoholism, for a period of one year after hepatic artery ligation. The patient has gained weight, and there has been no recurrence of the abdominal swelling.

Laboratory data before and after operation are listed in Table 2. The reaction to the Kahn serologic test was negative.

The patient was given a high-protein, low-fat, and low-salt diet. X-rays of the chest and of the esophagus with barium were normal. The electrocardiogram was interpreted as showing no diagnostic change. On the fifth hospital day, 3 daily intramuscular injections were begun,

Fig. 5 (Case 2).—Photomicrograph of liver biopsy specimen, showing Laennec cirrhosis and marked fibrosis of liver capsule; trichrome stain.

each of 400,000 units of penicillin and 1 gm. of streptomycin. On the sixth hospital day, paracentesis yielded 14,500 cc. of slightly cloudy, pale-yellow fluid.

On the ninth hospital day (Oct. 4, 1951), after the patient was given spinal anesthesia, the abdomen was opened and 2,000 cc. of pale-yellow fluid was removed. The liver was encased in a thick, smooth, pale-gray layer of fibrous tissue that extended over part of the parietal peritoneum. A needle connected to a water manometer was inserted into the portal

vein and the pressure was 31 cm. The common hepatic artery was occluded with double cotton ligatures. Approximately five minutes later, the water manometer was again connected to the portal vein, and the pressure was 34 cm. A biopsy specimen of the liver was taken, and the abdomen was closed. The patient tolerated the procedure well. Histologic examination of the liver revealed Laennec cirrhosis, with marked fibrosis of the capsule (Fig. 5).

The postoperative course was uneventful, except for marked enlargement of the liver that was most prominent 20 to 30 days after operation and slowly decreased so that it was approximately 8 cm. below the costal margin in the midclavicular line at the time of discharge. Paracenteses on the 13th, 19th, and 29th postoperative days yielded clear pale-yellow fluid in the amounts of 4,700 cc., 3,600 cc., and 2,800 cc., respectively. Strength, appetite, and sense of well-being improved, and the patient was discharged from the hospital after 52 days. He

Fig. 6 (Case 2).—Patient 38 days after hepatic artery ligation.

is now employed as a bartender, and his appearance 38 days after hepatic artery ligation is shown in Figure 6.

Comment.—Before operation an increased thymol turbidity of the serum was the single abnormal laboratory finding. After operation, cephalin flocculation remained negative, the plasma proteins showed no significant change, and there was only a slight and transient rise of the icterus index. At the time of the operation, it was difficult to identify the hepatic artery because of peritoneal fibrosis about the porta hepatis and because of a drop in blood pressure from spinal anesthesia, making palpation of the vessel difficult. The rise in portal vein pressure of 3 cm. of water five minutes after hepatic artery ligation is unexplained. However, the clinical results indicate that portal pressure was reduced. At the time of admis-

sion, the patient weighed 205 lb. (93.1 kg.) and was estimated to be accumulating ascitic fluid at the rate of 16,000 cc. per month. Ten paracenteses had been performed in the last 11 months. After hepatic artery ligation, three paracenteses during the first 29 postoperative days yielded a total of 8,100 cc. of fluid. Twenty-two days after operation, the patient weighed 176 lb. (79.9 kg.). He was discharged from the hospital 42 days after operation, and his weight at that time was 181 lb. (82.2 kg.). Since discharge, he has continued to feel well, his appetite is good, and he is employed as a bartender. The patient has not needed peritoneal aspiration to date (July 15, 1952), a period of eight months after discharge.

SUMMARY

The concept is held that portal decompensation in Laennec's cirrhosis, as manifested clinically by ascites and esophageal varices, is due in part to transmission of systemic arterial pressure from the hepatic artery to portal venules through anastomoses that develop in the perilobular fibrous connective tissue of the liver. Clinical application of this concept by ligation of the hepatic artery was of benefit in two patients with Laennec cirrhosis.

St. Luke's Hospital, Saginaw, Mich. (Dr. Smith).

INSIDIOUS THROMBOSIS OF THE AORTIC BIFURCATION

Report of Thirty-Five Cases

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AND
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THROMBOTIC obliteration of the aortic bifurcation has until recent years been considered a rare occurrence, and when it has been diagnosed the prognosis has been viewed with pessimism. Leriche in 1940 [1] aroused interest in this condition by publishing his observations on a number of patients who presented the typical symptoms and clinical features of what he termed "le syndrome de l'oblitération termino-aortique par artérite." Since then an increasing number of reports on patients with thrombosis of the terminal aorta have appeared (Elkin and Cooper,[2] Milanes, Perez-Stable, and Lastra,[3] Ortner and Griswold [4] and others [5]), and although not common this condition can hardly still be considered a rarity. Further, if the diagnosis is made early enough and proper treatment instituted forthwith, the prognosis is moderately good.

Thrombosis of the terminal aorta as described here is a condition which begins insidiously and progresses for a considerable time unnoticed, producing at first a narrowing of the aorta and only later a complete obliteration of that vessel. The gradual onset of the disease enables the patient to carry on for months, often for years, complaining only of mild and vague symptoms. It is not until late that alarming signs force him to consult a physician.

Thirty-five such patients were encountered at the clinic for peripheral vascular diseases in the eight-year period between 1944 and 1951. An analysis of their

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Dr. Beaconsfield is now with the Department of Surgery, Postgraduate Medical School of London.

1. Leriche, R.: De la resection du carrefour aortico-iliaque avec double sympathectomie lombaire pour thrombose artéritique de l'aorte: Le syndrome de l'oblitération termino-aortique par artérite, Presse méd. **48**:601, 1940.

2. Elkin, D. C., and Cooper, F. W., Jr.: Surgical Treatment of Insidious Thrombosis of the Aorta: Report of 10 Cases, Ann. Surg. **130**:417, 1949.

3. Milanes, B.; Perez-Stable, E., and Lastra, J. S.: Observations on Chronic Obstruction of the Abdominal Aorta, Surgery **28**:684, 1950. Mathivat, A.; Oudot, J., and Hatt, J. P.: Greffe artérielle de la fourche aortique, Arch mal. cœur **45**:356, 1952.

4. Ortner, A. B., and Griswold, R. A.: Chronic Occlusion of Bifurcation of the Aorta, Arch. Surg. **61**:793, 1950.

5. Burt, C. C.; Learmonth, J., and Richards, R. L.: On Occlusion of the Abdominal Aorta, Edinburgh M. J. **59**:65, 1952. Leriche, R., and Morel, A.: Syndrome of Thrombotic Obliteration of the Aortic Bifurcation, Ann. Surg. **127**:193, 1948.

cases has been set out in Tables 1 to 4, and we present an appraisal and discussion of the views now held as to the nature of the syndrome and its clinical management.

ETIOLOGY AND PATHOLOGY

The cause in this group of cases was arteriosclerosis in 28, inflammatory arteritis in 3, thromboangiitis obliterans in 2, syphilis in 1, and trauma in 1. The average age of the arteriosclerotic group was 52 years, which is younger than one would expect of this disease.

In two cases histological examination of the resected aorta showed changes consistent with a diagnosis of thromboangiitis obliterans. Further confirmation of

TABLE 1.—*Age and Sex Incidence*

Age	No. of Patients	Men	Women
30-40	4	4	0
40-50	17	15	2
50-60	12	12	0
Over 60	2	2	0
Total	35	33	2

TABLE 2.—*Symptomatology*

	No. of Patients
First symptom	
Pain	16
Fatigue in lower extremities	11
Impotence	6
Pallor of lower extremities	2
Total	35
Patients with early symptoms only	28
Patients with late and advanced symptoms	7
Symptoms present at time of diagnosis	
Pain	30
Fatigue in lower extremities	24
Pallor of lower extremities	18
Impotence	13
Global atrophy of lower extremities	10
Low back pain	10
Ulceration	4
Edema	3
Cyanosis	2
Dry gangrene	1

this diagnosis was available in one case when sections taken from the arteries of the leg amputated later through the midthigh also showed thromboangiitis obliterans. It is seldom thought that this disease affects the aorta and its main branches, but this case reemphasizes that thromboangiitis obliterans may be a generalized disease.

One patient had thrombotic obliteration from syphilitic aortitis, an interesting feature, as syphilis is usually associated with aortic aneurysm.

While the cause of insidious thrombosis of the aortic bifurcation is variable and may be any one of the many conditions causing arterial obliteration, the final

pathological picture is similar in all cases: There is a complete obliteration of the aortic bifurcation. The thrombus begins in one of two places: in one common iliac artery, spreading upward toward the aortic bifurcation and then invading both the aorta and the opposite common iliac artery, or in the aorta below the point of origin of the inferior mesenteric artery, spreading downward. From the pathological examination of the resected specimens and from the necropsy material, the former site appears to be three times more common than the latter.

The thrombus, which is often found to reach the aorta before it completely obliterates the common iliac artery, grows by extension along the wall, producing for some time only a narrowing of a considerable length of the vessel before complete occlusion occurs. This slow progress of the thrombus formation permits the collateral blood vessels to develop, and it is, therefore, not surprising that early symptoms are mild and often unnoticed.

In some instances the adventitia of the artery remains smooth and intact, but often there develops a perivascular infiltration around the thrombosed aorta, by which the vessel becomes adherent to the prevertebral fascia and the neighboring veins and lymph nodes, as well as to the sympathetic chain. In the late stage of the disease, when edema and ulcerations of the lower extremities develop, it is not unusual to find an associated peripheral venous thrombosis.

SYMPTOMATOLOGY

Thrombotic obliteration of the aortic bifurcation is almost exclusively seen in middle-aged men who, except for complaints related to the lower extremities, are usually in good health. The more gradual the obliteration, the better the collateral circulation, and the later and slower the onset of symptoms.

In the early stages of the disease, the patient consults the physician with one or more of the following symptoms: (1) Extreme liability to fatigue of both lower extremities. The fatigue will increase in severity and finally give way to actual weakness of the legs. (2) Pain, unilateral or bilateral, which is more in the nature of a dull ache than actual intermittent claudication. The pain may be present in the thigh, calf, or foot or in the entire lower extremity. It may be present while the patient is at rest and is always aggravated by exercise. (3) Low back pain. (4) Loss of sustained erection due to the poor blood supply to the corpus cavernosum.

Characteristically there is an absence of all arterial pulsation in both legs, clinically and oscillometrically, but slight oscillometric pulsation at the upper end of the thigh may be present when the collateral circulation is well developed, as in eight of our patients.

Pallor of the lower extremities is usually noticeable and often marked even when the leg is dependent. On elevation the leg blanches. Trophic changes in the skin or nails are seldom seen and when present are only slight.

Generalized wasting of the legs, usually present, is difficult to detect because it is symmetrical, but when questioned the patient often states that his legs are becoming thinner.

Hypertension is not characteristic of this disease, and in this series the blood pressure was found to range from 110/80 to 210/110 mm. of Hg, with an average of 160/90.

In the late stage of the disease, in addition to the aforementioned symptoms, all the typical features of the ischemic leg of advanced obliterative arterial disease are present. Severe and often intractable pain, edema, rubor, and finally ulceration and dry gangrene appear. Aortic thrombosis, although apparently well tolerated for years (five or even more), will if untreated always terminate in gangrene. The onset of this complication, most commonly seen over the pressure points—the toes, heels, malleoli, and around the knee joints and the trochanteric regions—is gradual and not always bilateral.

Fig. 1.—Aortic obliteration with good collateral circulation.

DIAGNOSIS

If this syndrome is kept in mind, the diagnosis is comparatively simple. When a patient complains of fatigue, pain, or coldness in his lower extremities or of impotence and the femoral pulses are found to be absent, then thrombosis of the aortic bifurcation should be suspected. Physical signs are so typical and so easy to elicit that no special investigations are necessary. It should be remembered that symptoms in insidious thrombosis never come on suddenly as they do in saddle embolus at the aortic bifurcation.

Except for coarctation of the aorta, which should present no problem in diagnosis, the only other condition which may cause similar symptoms and signs is obliteration of both common iliac arteries. In any event, since thrombosis of the aortic bifurcation usually begins in this way, and since the treatment of this condition is little different, the differential diagnosis is of no practical importance.

To confirm the diagnosis an aortogram may be made. This gives a precise picture of the site and size of the thrombus, the state of the arterial wall, and the extent of the collateral circulation. The prolonged period of mild symptoms of patients with this condition can be explained by the anastomotic channels (Fig. 1).

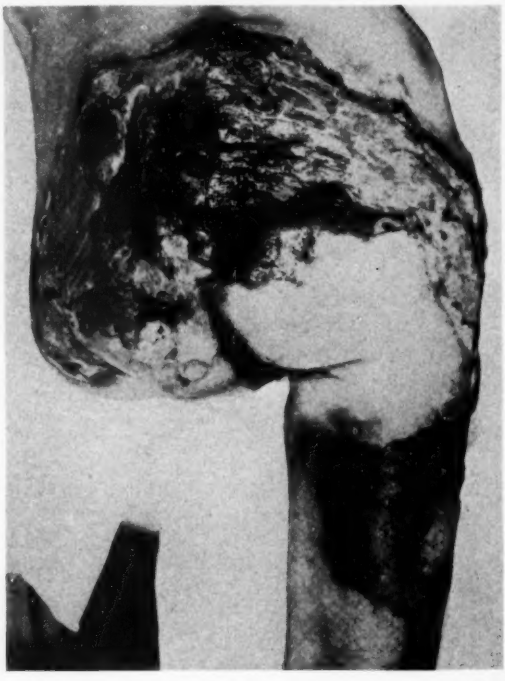

Fig. 2.—Patient with thrombosis at the bifurcation of the aorta, with gangrene of both legs, the buttocks and the pelvis. This photograph is from *Angiology* (**2**:517, 1951) and is reproduced through the courtesy of Dr. G. H. Pratt.

Aortography was performed for 31 of the 35 patients discussed here, and all the aortograms showed complete obliteration of the terminal aorta.

PROGNOSIS

A favorable prognosis rests on early diagnosis and treatment. It depends partly on how soon after the onset of symptoms the patient first consults the physician and partly on the speed with which the condition is recognized and properly treated. In our cases the average period elapsing between the onset of symptoms and the time the patient sought medical advice was 4 years, the shortest interval being 6 months and the longest 21 years.

Of the 35 patients, 25 were between the ages of 38 and 42 at the onset of their symptoms, the youngest being 27 and the oldest 57.

Treatment will in many cases restore the patient to almost normal health, and even when treatment does not relieve all the symptoms it may at least arrest the progress of the disease. The age of the patient cannot be used as a criterion for prognosis. Without treatment the prognosis is poor and the patient will sooner or later have to undergo a bilateral above-knee amputation (Fig. 2). Otherwise he may die of hypertension and uremia resulting from extension of the thrombus to involve the orifices of the renal arteries.

TABLE 3.—*Results of Treatment*

Type of Treatment	No. of Patients	Results				
		Good Results	Improvement	No Change	Patient Worse	Patient Died
Patients with early signs and symptoms (28)						
Bilateral lumbar sympathectomy and aortectomy	9	3	5	0	0	1*
Bilateral lumbar sympathectomy	14	0	11	2	0	1†
Bilateral lumbar sympathectomy blocks	1	0	0	1	0	0
No treatment	4	0	0	1	2	1†
Total	28	3	16	4	2	3
Patients with late signs and symptoms (7)						
Bilateral lumbar sympathectomy	7	0	1	6	0	0
Total	35	3	17	10	2	3

* Patient died postoperatively.
† Patient died of renal complications.

TABLE 4.—*Follow-Up of Patients from One to Eight Years After Treatment*

Initial Treatment	No. of Patients	Subsequent Treatment	
		None	Amputation
Early cases			
Bilateral lumbar sympathectomy	13	12	1
Bilateral lumbar sympathectomy and resection of the aortic bifurcation	8	7	1
Late cases			
Bilateral lumbar sympathectomy	7	1	6

TREATMENT

Although the treatment of thrombotic obliteration of the aortic bifurcation may vary a little from clinic to clinic, the principles remain the same. These are bilateral lumbar sympathectomy to improve the circulation to the limbs, followed, when possible, with resection of the thrombosed portion of the terminal aorta and common iliac arteries, and, finally, amputation of a portion of the extremity if this becomes necessary because of gangrene.

The results of treatment based on these principles as judged by follow-up periods of one to eight years, are given in Tables 3 and 4. The results have been classified as good in patients who made a complete clinical recovery and as improved in those who recovered only partially but sufficiently to resume their daily occupation, live a normal life, and visit the physician only for follow-up purposes.

If bilateral sympathectomy alone is done, it can be performed as a one-stage operation provided the general condition of the patient is satisfactory. The second, third, and fourth lumbar sympathetic ganglia are removed through a transperitoneal medial incision. This approach will conserve some of the collateral arteries running in the muscles of the flanks. On the other hand, if the aorta is to be resected, it is usually wiser to do the operation in two stages, performing a right lumbar sympathectomy first and removing the left sympathetic chain and the aortic bifurcation through an extraperitoneal iliac approach one or two weeks later. In most instances the final decision as to whether the aortic bifurcation is to be resected or not is made at operation. For this reason, most of our patients had the two-stage operation.

Fig. 3.—Resected segment of the aortic bifurcation.

The removal of the thrombosed segment is desirable whenever possible (Fig. 3) because in some cases the thrombus continues to grow, endangering not only the collateral circulation but also the renal vessels. One of our patients died from this complication two years after bilateral lumbar sympathectomy. Also, if the thrombosed aorta is not removed the patient will often continue to have low back pain, which is probably due to the associated periarteritis.

Experience has shown that periarterial sympathectomy alone, when done for arterial thrombosis, gives some relief of pain and spasm in the collateral blood vessels. Therefore, arteriectomy in aortic thrombosis must of necessity add the benefit of a periarterial sympathectomy. In some of our patients with extensive thrombosis of the aorta and common iliac arteries, it was impossible to reach above the thrombus with any reasonable degree of safety. We therefore resected only the aortic bifurcation and the iliac arteries, leaving a part of the thrombus still lodged in the terminal aorta. The immediate relief of lumbar pain following even this limited removal seems, in our opinion, to justify this procedure.

There are some contraindications to resection of the aortic bifurcation. These are: (1) Advanced arteriosclerosis with a markedly calcified aorta, the extent of which can be determined by palpation at operation. In these circumstances the elasticity of the aortic wall has almost completely disappeared and it is impossible to ligate and suture the proximal end of the aorta satisfactorily. (2) Extensive periarteritis found at operation. Removal of the terminal aorta from a bed of dense adhesions containing some of the vital collaterals is unwise.

The general condition of the patient must be carefully assessed if resection of the aorta is anticipated. Bilateral lumbar sympathectomy alone disturbs the patient little, and postoperative recovery is usually uneventful. Resection of the aorta,

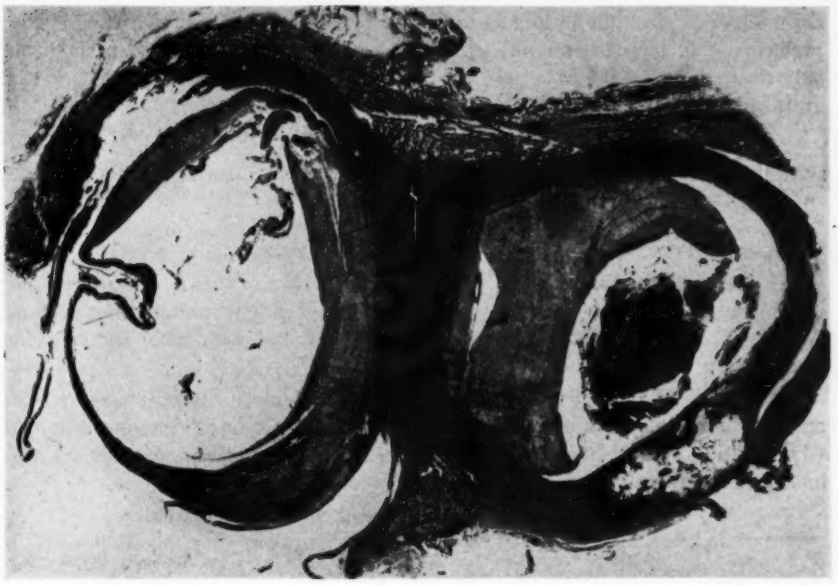

Fig. 4.—Photomicrograph of the thrombosed bifurcation (Fig. 3) showing periarteritis, thickening of the vessel wall, and thrombosis of the lumen.

on the other hand, is a major procedure which may produce severe shock, most apparent during the dissection of the vessel from its bed.

In these patients, with such a slender arterial supply to the lower limbs, it is desirable to attempt to improve the collateral circulation as much as possible by lumbar sympathectomy before any further surgical step is undertaken; otherwise healing will be delayed or may not take place at all. When gangrene of the legs has already developed and an amputation is inevitable, it is essential to do a lumbar sympathectomy prior to the amputation, because without this the stump does not heal. Incidentally, it would be wise in such cases to make this operation a prelude to any other surgical procedure which it may be necessary to perform on the legs, such as reduction of a compound fracture.

In this series seven patients were first seen in the late stage of the disease, when advanced trophic changes in the lower limbs were already present. In them

the results of treatment were not good. Only one patient improved; the condition of the remaining six was unchanged and they had to have an amputation later.

Twenty-eight patients were first seen in the early stage of the disease; four refused treatment, and of these, the condition of one remained unchanged, two became worse, and one died. The remaining 24 were surgically treated; of these, 2 died, one postoperatively and the other from renal failure, 2 years after bilateral lumbar sympathectomy; the condition of 3 remained unchanged; 16 improved, and 3 became symptom-free.

It must be admitted that the present methods of surgical treatment of insidious thrombosis of the aortic bifurcation are not entirely satisfactory, and the success of the aortic-graft replacement in coarctation and in aneurysm of the abdominal aorta suggests that this procedure might be a more rational way of tackling the problem. This approach was originally suggested by Leriche thirty years ago but only realized during the past year, when Oudot [6] reported successful resection and grafting of the thrombosed aortic bifurcation in three patients.

SUMMARY

A review of 35 cases of insidious thrombosis of the aortic bifurcation is presented.

Arteriosclerosis is the commonest cause of the disease.

The symptoms are fatigue, pain and weakness in the lower limbs, and impotence, all appearing gradually and progressing slowly for months or years. Absence of arterial pulsations in both lower limbs is found, with pallor and wasting; ulcerations and gangrene appear late in the disease.

The choice of treatment is between (1) bilateral lumbar sympathectomy with resection of the aortic bifurcation, (2) bilateral lumbar sympathectomy alone, and (3) resection and grafting of the thrombosed aortic bifurcation with or without lumbar sympathectomy.

A good prognosis depends on early diagnosis and prompt treatment.

6. Oudot, J.: La greffe vasculaire dans les thromboses du carrefour aortique, Presse méd. **59**:234, 1951.

THROMBOSIS OF THE AORTIC BIFURCATION TREATED BY RESECTION AND HOMOGRAFT REPLACEMENT

Report of Five Cases

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AND
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Le traitement idéal consisterait evidemment à réséquer la zone obliterée et à rétablir si possible la perméabilité artérielle.—*Leriche.*[1]

THE IDEAL treatment of arterial thrombosis is the replacement of the obliterated segment with a vascular graft. With this thought in mind, we have tackled the problem of insidious thrombosis of the aortic bifurcation. Five patients with this condition have been treated during the last two years, the aortic bifurcation being replaced by a homograft. The results are encouraging. To the best of our knowledge these are the first successful cases of this type, and the details are worth recording.

PREOPERATIVE CONSIDERATIONS

Once the diagnosis of thrombosis of the aortic bifurcation is made and confirmed by an aortogram, three points must be considered before grafting is decided upon: (*a*) the general condition of the patient, (*b*) the patency of the large arteries of the thigh and calf below the block, and (*c*) the preparation of the graft.

All the usual precautions which precede a major surgical operation must be taken when considering the general condition of the patient. Resection and grafting of the thrombosed aortic bifurcation is a long procedure. It may produce severe shock during the dissection of the adherent aorta from its bed or immediately after the completion of the operation, when the circulation through the graft has been reestablished. Hence, careful evaluation of the cardiac and renal functions before the operation are essential. Phenolsulfonphthalein renal function tests and urea clearance are carried out as part of the routine procedure and also, if necessary, an intravenous pyelogram. The age of the patient is not as important as his general state of well-being. The procedure is possible provided the calcification of the aorta is not marked.

A day or two before the operation, the femoral arteries are exposed under local anesthesia and an arteriogram carried out. A direct exposure of the vessels will

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1. Leriche, R.: De la résection du carrefour aortico-iliaque avec double sympathectomie lombaire pour thrombose artérique de l'aorte: Le syndrome de l'oblitération termino-aortique par artérite, Presse méd. **48**:601, 1940.

permit the arterial wall to be seen and its suitability for anastomosing assessed. The roentgenogram obtained by retrograde injection of the dye will show the exact length of the obliteration of the iliac vessels.

The homograft used is removed under aseptic conditions not later than four hours after death. All branching vessels of the removed aorta above its bifurcation are carefully ligated. The graft is then well washed through to remove all the blood and clots which might have remained in the lumen. After this, the graft is preserved at 4 C. in an isotonic solution to which penicillin and streptomycin and 10% blood serum have been added. The graft is not used unless numerous cultures are sterile.

OPERATIVE TECHNIQUE

Incision.—There are two possible approaches to the terminal aorta—through a midline transperitoneal incision or by a left extraperitoneal iliac incision. The first one has the advantage of giving an excellent view of the terminal aorta without injuring the collateral arteries running in the muscles of the flanks. On the other hand, however, this approach presents some major inconveniences. Firstly, this exposure is inadequate if the anastomosis has to be performed at a high level just below the renal arteries or at the distal end of the external iliac arteries. Secondly, there is always the risk of oozing from the aortic bed, which may produce a hematoma, and blood in the peritoneal cavity may produce an ileus. For these reasons we prefer the wide exposure obtained through a left extraperitoneal iliac approach, with extension of the incision upwards and resection of the 10th or 11th rib. If the anastomosis on the right side is below the level of the common iliac artery, an additional low right extraperitoneal iliac incision is made to facilitate this part of the operation. Finally, if the inferior anastomosis is at the level of the femoral artery, we prefer to make an incision over this artery and place the graft in a tunnel-like fashion through the femoral ring.

Dissection and Resection of Aorta.—To expose the aorta, the peritoneum is separated and retracted in a medial and slightly upward direction, starting at the dorsal end of the incision. Its dissection is usually difficult, owing to the periaortitis which is typical of the disease. The removal of the thrombosed segment should therefore be started in the region of the iliac vessels and continued upward. The common iliac arteries are cut first, facilitating the dissection of the posterior wall of the aorta by lifting it upward, taking great care not to injure the vena cava to which it is often extremely adherent.

When the thrombus in the aorta extends to the level of the right renal artery, an aortic clamp is placed between the two renal arteries, and the vessel is then cut 2 or 3 cm. below the right renal artery through the thrombus itself. A thromboendarteriectomy is then performed, removing the remaining portion of the thrombus which is left in the lumen of the aorta just distal to the renal vessels. If the aorta is amputated too close to the renal arteries, there is always the danger of injuring them during the anastomosis.

Anastomosis of the graft is performed in the following order: (*a*) with the main aortic trunk; (*b*) with the left iliac or femoral artery, according to circumstances, and (*c*) similarly on the right side. The graft is supported by two or three stay sutures and the anastomosis performed using interrupted everted mattress stitches, 0000 nonabsorbable surgical (silk) sutures for the aorta and 00000 silk for the iliac arteries. The wound is always drained through a loin stab incision.

Anesthesia and the Immediate Postoperative Period (Dr. Raymond Alluaume).—The operation begins by anesthetizing the patient with intravenous injections of thiopental (pentothal®) sodium and curare, after which an intratracheal tube is passed. The anesthetic used is ether and oxygen. In Cases 1 and 2, although a generous quantity of procaine hydrochloride was used to saturate the hypogastric plexus, there was considerable oscillation in the blood pressure during the dissection of the adherent aorta from its bed. Moreover, there was a marked drop in the blood pressure when the aortic circulation was reestablished after the completion of the graft, in spite of intra-aortic blood transfusion.

To overcome this difficulty, we resorted to the use of ganglioplegic agents in combination with hypothermia. The ganglioplegic agent gives rise to vasodilatation, which state responds

easily to refrigeration. This technique has enabled us to operate on two patients who were over 60 years of age without ill effects. The patient is refrigerated by placing ice packs from his waist down, starting two hours before the operation. Three hours before the induction of anesthesia, he is given 0.75 gm. of phenothiazine ("phenergan"), an antihistaminic compound. This is followed an hour later by the administration of 0.1 gm. of meperidine hydrochloride ("dolosal," similar to demerol®) together with a ganglioplegic agent which is injected intramuscularly (also if necessary, intravenously), allowing the blood pressure to drop to between 90 to 100 systolic. This level is maintained. If the blood pressure falls lower during the operation, the patient is placed in the Trendelenburg position. Refrigeration is continued throughout the operation, the temperature being maintained between 35 and 36 C. After the operation the body temperature is allowed to rise slowly and is kept between 36.5 and 37.5 C., if necessary with ice packs. If the blood pressure varies considerably, it can be stabilized by giving another injection of the ganglioplegic agents and meperidine.

Anticoagulants.—As soon as the anastomosis is started, the patient is heparinized. The blood clotting time is maintained at 15 minutes and is checked every two hours for three days. During this period the patient receives an uninterrupted slow intravenous drip to which varying quantities of heparin are added.

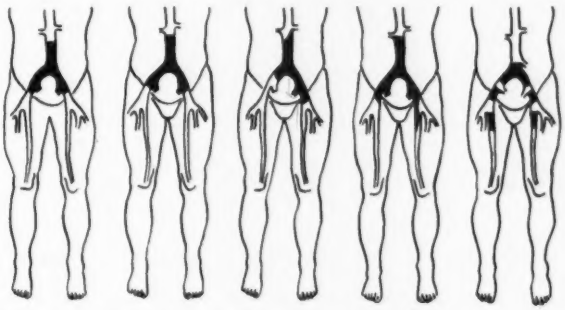

Fig. 1.—Extent of thrombosis as seen at operation in five patients.

REPORT OF CASES

The main symptoms and signs, as well as the oscillometric readings, arterial pulsations, and skin temperatures before and after operation for all five patients are set out in Tables 1, 2, 3, and 4. The extent of the thromboses, as seen at operation, will be found in Fig. 1.

CASE 1.—A 51-year-old woman was seen in the outpatient clinic, complaining of progressive weakness and pain in both legs for the past two years. At the time of her visit she also had pain at rest in both lower extremities, more marked on the left side. She had been in excellent health prior to her present illness, except that 25 years previously a diagnosis of syphilis had been made. Treatment had been given, and at the time of admission to hospital, the Wassermann reaction was negative.

On physical examination all pulses and oscillometric readings in both lower extremities were absent; the legs were cold and pale. There was a small gangrenous plaque in the region of the left lateral malleolus. The blood pressure was 140/70 mm. of Hg, and on examination of the fundi the retinal vessels showed a moderately advanced arteriosclerosis. The blood urea and phenolsulfonphthalein test were negative. An aortogram showed complete obliteration of the aortic bifurcation, but the arteriogram of the femoral arteries showed good filling below the block (Fig. 2).

Operation was performed on Nov. 14, 1950. The aorta was approached through a left extraperitoneal iliac incision, with the resection of the 10th rib. The thrombosed segment was resected, starting at the level of the external iliac arteries to 2 cm. below the renal vessels. A homograft

taken 24 days previously was used. The anastomosis between the aorta and the graft and between the left external iliac artery and the graft gave no difficulty, but the anastomosis on the right side was unsatisfactory, since the exposure of that region was incomplete. After the operation,

TABLE 1.—*Symptoms and Signs*

Case No.	Age, Yr.	Sex	Pain	Trophic Changes	Able to Walk, Yd.	Loss of Sustained Erection	Atrophy	Duration of Symptoms, Yr.	Previous Treatment
1	51	F	++	++	40	..	Marked	2	Medical
2	52	M	+	0	150	+	None	1	Medical
3	45	M	+	0	100	+	None	11	Bilateral lumbar sympathectomy
4	63	M	+++	++	20	+	Marked	3	Right lumbar sympathectomy
5	64	M	++	+	15	+	Marked	2	Medical

TABLE 2.—*Arterial Pulsation Before and After Operation*

Location	Case 1		Case 2		Case 3		Case 4		Case 5	
	Before	After	Before	After	Before	After	Before	After	Before	After
Right femoral artery	0	0	0	+	0	+	0	+	0	+
Right popliteal artery	0	0	0	+	0	+	0	+	0	+
Right dorsalis pedis artery	0	0	0	+	0	+	0	+	0	0
Left femoral artery	0	+	0	+	0	+	0	+	0	+
Left popliteal artery	0	+	0	+	0	+	0	0	0	+
Left dorsalis pedis artery	0	+	0	+	0	+	0	0	0	+

TABLE 3.—*Oscillometric Readings Before and After Operation*

Location	Case 1		Case 2		Case 3		Case 4		Case 5	
	Before	After	Before	After	Before	After	Before	After	Before	After
Right thigh	0	0.5	0	3.0	0	3.0	0	5.0	0	1.0
Right calf	0	0.25	0	1.5	0	1.5	0	2.0	0	0.25
Left thigh	0	3.0	0	3.0	0	5.0	0	3.0	0	2.0
Left calf	0	2.0	0	1.5	0	3.0	0	0.5	0	1.5

TABLE 4.—*Skin Temperature* Before and After Operation*

Case No.	Big Toe			
	Before		After	
	Left	Right	Left	Right
1	22.5	24.0	32.2	28.0
2	24.2	25.0	32.4	32.8
3	33.0	31.5	Not taken	
4	22.5	27.0	32.5	33.0
5	20.5	21.0	31.0	28.0

* Measured in degrees Centigrade.

the patient made an uneventful recovery. There was, however, an increase of blood urea to 120 mg. per 100 ml., which decreased to 25 mg. per 100 ml. in the next six days. All pulses were now present in the left leg but none in the right. Aortography performed a few weeks later showed a normal filling of the arteries of the left lower extremity but none on the right. To correct this, the patient was reexplored on May 8, 1951, and an arterial graft placed, anasto-

mosing the now patent left external iliac artery to the right external iliac artery in a bridge-like fashion. At the end of the operation, both the graft and the right femoral artery showed good filling.

After the first operation the graft was patent on the left side, and the left leg showed immediate improvement. The gangrenous area at the ankle healed after a few weeks, the pain at rest disappeared, and the skin temperature increased. The pulses and oscillometric readings,

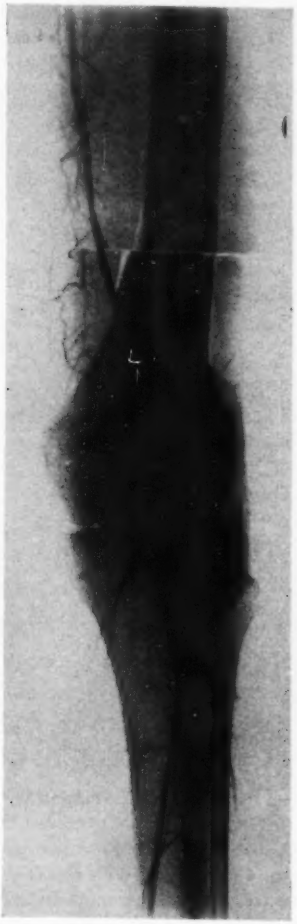

Fig. 2 (Case 1).—Arteriogram of femoral artery, showing good filling of arteries of leg below block.

absent before the operation, returned all the way down the leg. On the right side, where the iliac anastomosis thrombosed, the extremity showed no noticeable improvement in spite of the removal of the original thrombosed iliac artery. This case points out that arteriectomy alone, when it concerns a large artery, is not a satisfactory treatment and is performed without a sympathectomy or arterial graft. After the second operation, which reestablished the blood flow through the right external iliac artery, the pain at rest in the right leg disappeared. When seen recently, the patient could walk for half a mile without discomfort.

CASE 2.—A 52-year-old man was admitted to the hospital complaining of severe intermittent claudication after walking less than 150 yd. (135 meters) and of moderate pain at rest for the previous few weeks. He had had progressive pain and weakness in both lower extremities for the past 11 years. He was a heavy smoker.

On physical examination all pulses and oscillometric readings were absent in both legs, but there were no trophic changes. The Wassermann reaction was negative. The eye fundi were normal. There was a coronary lesion discovered by routine electrocardiography with inversion of the T wave in lead III. The urea clearance was within normal limits. The chest x-rays revealed no abnormalities. The heart was not enlarged, and there was no apparent lung pathology.

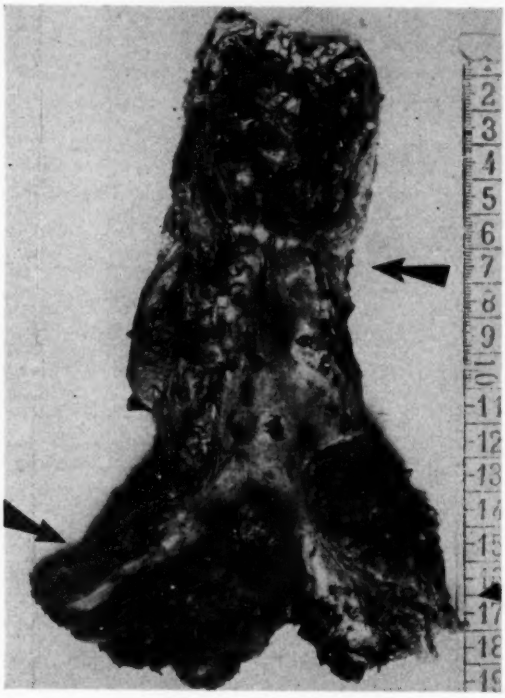

Fig. 3 (Case 2).—Postmortem specimen of aortic bifurcation. Arrows show line of suture.

Operation took place on May 16, 1951. The aorta was approached through a left extraperitoneal incision, with resection of the 10th and 11th ribs. There was an extensive periaortitis. The aortic bifurcation was resected from the proximal end of both external iliac arteries to 3 cm. below the right renal artery. An aortic bifurcation graft taken 21 days earlier was used. In order to have a better exposure for the anastomosis on the right side, a right extraperitoneal iliac incision was made after completing the anastomosis between the graft and the aorta and between the graft and the left external iliac artery.

The result of the operation was satisfactory: The femoral, popliteal, and dorsalis pedis arteries were pulsating. Oscillometric readings, absent before operation, were now present.

The operation gave good results on both sides, due to the double extraperitoneal approach. An examination four months after operation elicited the presence of all pulses in both lower extremities (Table 2). The patient was readmitted to the hospital seven months after grafting, this time because of pulmonary tuberculosis. In spite of all available treatment he died a few

weeks later of miliary spread. On postmortem examination the graft was found to be patent; the lumen contained no thrombus, and the wall revealed no apparent weakness or aneurysm (Fig. 3).

Microscopic examination of the specimen of the graft, however, showed that the smooth muscle fibers of the media had degenerated and the elastic fibers had become fragmented. Similar changes have been observed in grafts on experimental animals at the end of five or six months after the operation.

CASE 3.—A 45-year-old man was admitted to the hospital complaining of pain occurring in the thigh, calf, and foot of both legs after walking 100 yd. (90 meters). This was more marked on the left side. Walking had become more difficult in the past few months, and he had lost all ability to maintain penile erection. The patient was a heavy smoker. A bilateral lumbar sympathectomy carried out one year before the present admission had given no results other than increasing the temperature of the feet. An aortogram showed partial obliteration of the lumen at the level of the right renal artery, and complete obliteration 4 cm. lower down. The large arteries of thigh and calf were patent. The patient's general condition was good. Laboratory investigation revealed normal cardiac and renal functions.

Operation was performed on Nov. 14, 1951. The aorta was approached and dissected through a left extraperitoneal iliac incision. It was then compressed between the two renal arteries and amputated at a level 2 cm. below the right renal artery. After this, a local endarteriectomy of the partially obliterated remaining portion of the aorta just below the renal vessel was performed. After the main anastomosis was completed, the graft, which was 11 days old, was anastomosed on the left side with the common femoral artery, and on the right, with the distal end of the common iliac artery. After the operation, anuria developed for 36 hours, and the blood urea rose to 200 mg. per 100 ml. On the fifth postoperative day the patient passed 1,200 cc. of urine, and the blood urea returned to normal on the eighth day.

The patient was last seen in September, 1952, and he was then able to walk more than half a mile, had returned to his normal occupation, and had regained his sexual powers.

This case clearly illustrates the advantages of resection and grafting over sympathectomy. After bilateral lumbar sympathectomy in 1950, the patient's improvement was only slight, and, although the skin temperature of his legs increased, the symptoms of pain were still present.

In this case we used only one incision, namely the left extraperitoneal iliac approach. This gave sufficient exposure to anastomose the graft and the common iliac artery on the right side without difficulty. Figure 4 shows the aortogram six months after resection and grafting. It reveals the patency of the graft and good filling of the large vessels below.

CASE 4.—A 63-year-old man complaining of progressive intermittent claudication since 1949 was first seen in the outpatient clinic in January, 1952. He had had a right lumbar sympathectomy early in 1950, resulting in some improvement, but by the end of that year the symptoms recurred, and at the time of admission to the hospital he was able to walk only 20 yd. (18 meters). He also complained of nocturnal and rest pain as well as edema and ulceration in the region of the left ankle since December, 1951. The patient was a heavy smoker.

On examination, all pulses and oscillometric readings in both lower extremities were absent, and the symptoms and signs of advanced ischemic limbs were present. The patient's general condition was satisfactory.

Aortography revealed thrombosis starting at the level of the right renal artery. The right femoral artery was patent but showed advanced atheromatous lesions. On the left the common femoral artery was thrombosed, but the profunda femoris was patent and well filled with blood, due to the rich collateral circulation.

Operation was performed on April 16, 1952. After the usual incision and exposure of the thrombosed segment of the aorta, a clamp was placed between the renal arteries and the aorta sectioned 4 cm. below, permitting the removal of the thrombosis in the remaining distal end of the aorta. After the completion of this part of the operation, it was noticed that the right renal artery was partially occluded by the growing thrombus from the aorta. Therefore endarteriectomy of the right renal artery was also performed. The anastomosis was then carried out between the graft and the portion of the aorta from which the thrombus had just been removed by

endarteriectomy, followed by anastomosis on the left with the deep femoral artery and on the right with the common femoral artery through an additional right extraperitoneal iliac incision. The graft used was 17 days old.

The postoperative course was uneventful. Pulses and oscillometric readings were now present on both sides; the edema of the leg disappeared, and the ulcer healed.

Clamping of the aorta between the renal arteries to permit a high anastomosis and endarteriectomy of the partially thrombosed right renal artery produced no ill effects, and the urea did not increase after the operation. This case also shows that anastomosis between the graft and the deep femoral artery is possible and gives satisfactory results.

CASE 5.—A 64-year-old man complained of progressive intermittent claudication of two years' duration. At the time of admission in April, 1952, the patient could walk only 10 to 15 yd. (9 to

Fig. 4 (Case 3).—Aortogram made six months after resection and grafting, revealing patency of graft and good filling of large vessels below.

13.5 meters). The right big toe was continuously painful and showed the signs of early gangrene. The patient was a heavy smoker. His general condition was satisfactory, and an aortogram showed complete obliteration of the terminal aorta.

At operation on May 15, 1952, a left extraperitoneal iliac approach was used, with resection of the 11th rib. The aorta was thrombosed below the inferior mesenteric artery. The internal iliac arteries were patent, but both proximal ends of the external iliac arteries, as well as the superficial femoral arteries, were almost completely thrombosed. Therefore after resection of the aortic bifurcation only, the anastomosis was performed between the aorta and the graft below the inferior mesenteric artery and distally with the right and left common femoral arteries with

a 22-day-old graft. Endarteriectomy of the external iliac and femoral arteries was considered during the operation, but was decided against, since the areas were extensive and would leave a large surface of injured intima susceptible to new thrombus formation. To resect all of the thrombosed segments would have been inadvisable.

Immediately following the operation, both popliteal vessels pulsated and the color and temperature of the extremities improved. The postoperative course was uneventful, and at the time of discharge the patient was able to walk 500 yd. (450 meters) without difficulty.

COMMENTS

Replacement of the thrombosed aortic bifurcation with a homograft has given good results. This surgical procedure is still in its infancy and not enough time has passed since the operations were performed to assess the long-term results. Nevertheless, a certain number of conclusions can be drawn.

Grafting of the aortic bifurcation has thus far proved to be a better surgical procedure than sympathectomy and arteriectomy alone. It reestablishes the main arterial current to the lower limbs, and immediately following the completion of the anastomosis the color and temperature of the legs approach normal. Pulses of the femoral and popliteal arteries, as well as the oscillometric readings, return, as can be seen in Table 1. Cases of ulceration heal rapidly after the operation. Edema and trophic changes, which may have been present before the operation, disappear. The four surviving patients were last seen in September, 1952, and they showed no impairment of the circulation of the lower limbs.

In the early stage of the disease before trophic changes have occurred, lumbar sympathectomy, with or without resection of thrombosed vessels, gives fairly good results. But sympathectomy performed when ulceration and gangrene have already supervened will not, in most instances, improve the patient sufficiently to prevent a final amputation above the knee. We consider therefore that any phase of the disease, and particularly the advanced one, requires immediate grafting to give any hope of saving the limb. Cases 1, 4, and 5 illustrate this point.

It may be difficult to decide whether or not a lumbar sympathectomy should be performed concurrently with resection and homograft replacement. If we could be certain that the graft would remain patent, sympathectomy would be unnecessary, but, since most of these patients suffer from arteriosclerosis, removal and replacement by a graft of the thrombosed segment would not, in itself, affect the pathological process. This process might, at some later date, produce obliteration of the graft or of some more distal vessel of the limb. Sympathectomy should therefore be performed at the same time as resection and grafting, since possible reexploration in the future would be extremely difficult because of marked scar formation in the region of the graft and the surrounding tissues.

SUMMARY

A new method of treating insidious thrombosis of the aortic bifurcation by means of resection and homograft replacement is described.

Five patients with this disease have been treated in this manner with good results during the past two years. Symptomatically, they have all much improved. The toe skin temperature increased; arterial pulsation and oscillometric readings, absent in the lower extremities before the operation, returned.

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VAGOTOMY

Follow-Up of One Hundred Cases

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WITH OPINIONS concerning the proper treatment of intractable peptic ulcer still varying so widely, further reports of carefully followed series of vagotomies are necessary. After having performed 620 vagus sections, Dragstedt [1] is convinced that this operation combined with a small posterior gastroenterostomy should replace subtotal gastric resection in the treatment of duodenal, marginal, and some esophageal ulcers. Crile [2] is equally enthusiastic after performing 257 vagotomies and gastroenterostomy without a death and with only three failures in the first 100 patients followed for 18 months or longer. Grimson [3] feels that complications or side-effects limit the usefulness of vagotomy more than the occasional failure of an ulcer to heal. Walters [4] questions whether it is necessary or possible to sever all vagus fibers, since he has noted 10 to 20% positive insulin tests postoperatively. He now uses the operation for recurring ulceration after adequate partial gastrectomy and feels that it has little place alone in the treatment of duodenal ulcers.

The material for the present study consists of the first hundred patients with vagotomy performed at the Crile Veterans Administration Hospital between June, 1946 and August, 1949. Of these patients, 96% have been followed by readmission

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1. Dragstedt, L. R., and Woodward, E. R.: Appraisal of Vagotomy for Peptic Ulcer After 7 Years, J. A. M. A. **145**:795, 1951.

2. Crile, G., Jr.: Surgical Treatment of Duodenal Ulcer: A Comparison of the Results of Treatment With and Without Vagotomy, Rev. Gastroenterol. **17**:781, 1950.

3. Grimson, K. S., and others: Vagotomy: Observations During 4 Years, Surgery **27**:49, 1950.

4. Walters, W.; Belding, H. H., and Lillie, W. I.: Physiological and Clinical Studies of Vagotomized Patients: A Study of 331 Patients, A. M. A. Arch. Surg. **62**:183, 1951.

to the hospital for repeat x-ray examination and physiologic studies. An additional 2% have been followed by questionnaire. Hospital admissions varied from one to eight in number, with the first follow-up in from three to six months and subsequent follow-ups at yearly intervals. Eighty-eight patients had multiple hospital admissions, and 70 of these were seen within the last year. Eighty-five per cent of the patients were followed for between two and six years. Once the results in a case were proved a failure by demonstration of a recurrent ulcer either by x-ray or reoperation, further follow-up for the vagotomy patient was not deemed essential. There were several patients who did not report for follow-up between their six-month visit and their current one within the past year. Some of these responded to questionnaires during the interim.

PREOPERATIVE PATHOLOGY

The patients selected for vagotomy were those with complicated peptic ulcers, referred for surgery by the medical service during the period of the study. No

TABLE 1.—*Preoperative Pathology*

Type of Ulcer		No.
Duodenal ulcer		80
Intractable	24	
Hemorrhage	20	
Obstruction	18	
Perforation	9	
Combinations	9	
Gastric ulcer		8
Marginal ulcer		12
Following gastroenterostomy	7	
Following gastric resection	5	

patient with acute hemorrhage was vagotomized. Patients with duodenal ulcers, marginal ulcers, and gastric ulcers were included in the series. There were a small number of associated duodenal and gastric ulcers which were considered as duodenal ulcers.

The cases of duodenal ulcers were classified according to their chief presenting complication, such as hemorrhage, perforation, obstruction, etc. (Table 1). When two or more such complications were present, the case was classified as a combination. A patient was considered to have an intractable ulcer when his symptoms could not be controlled by proper medical management in the hospital, or when economic and social factors prevented his continued health outside the hospital for more than a short time. Acute perforations were merely closed and definitive surgery undertaken at a later date.

The small group of gastric ulcers had all failed to heal within four weeks under medical management in the hospital. Most of them were on the lesser curvature in the prepyloric region. Two of these ulcers were high on the lesser curvature and required associated gastroenterostomy to empty the gastric pouch above the lesion. One patient, who was vagotomized for a high gastric ulcer, was discovered to have gastric carcinoma and has been excluded from this series.

Seven of the marginal ulcers occurred after previous gastroenterostomy and five after gastric resection. One of the ulcers that followed gastroenterostomy had produced a gastrojejunocolic fistula, which was treated by vagotomy and closure of the fistula, with restoration of normal anatomical relationships.

TYPES OF OPERATIONS

In the first 50 patients operated upon in 1946 and in part of 1947 the procedure was done transthoracically, except for one patient with a duodenal ulcer and two with gastric ulcers that obviously needed supplementary drainage operations. Five patients with obstructed duodenal ulcers were treated by gastroenterostomy several weeks before transthoracic vagotomy, and these cases have been classified as cases of vagotomy and gastroenterostomy (Table 2).

In the majority of the second 50 patients operated upon in the balance of 1947, 1948, and up until August, 1949, the procedures were done subdiaphragmatically. The decision to do an associated gastroenterostomy was made at the time of explora-

TABLE 2.—*Operations Performed*

	Vagotomy		Vagotomy and Gastroenterostomy	
Duodenal ulcer*		46		33
Intractable	20		4	
Hemorrhage	15		5	
Obstruction	2		16	
Perforation	5		4	
Combinations	4		4	
Gastric ulcer		6		2
Marginal ulcer		12		
Following gastroenterostomy	7			
Following gastric resection	5			

* One duodenal ulcer with high free-acid levels was treated by vagotomy and subtotal gastric resection.

tion on the basis of apparent obstruction. As the series progressed, the addition of an anterior gastroenterostomy became much more frequent, but it was not performed routinely.

Patients with marginal ulcers, in general, were operated upon transthoracically. One patient who was revagotomized subdiaphragmatically along with additional resection after the marginal ulcer had recurred was not included for the second procedure.

One patient with very high preoperative free-acid levels was treated with a three-quarter gastric resection and subdiaphragmatic vagotomy (Palumbo [5]).

RESULTS

Results have been classified according to preoperative pathology, the type of operation performed, and the result obtained.

A patient was considered to have a "good" result when he had essentially no gastrointestinal complaints, was eating a full diet without medication, and had no

5. Palumbo, L. T.; Marquis, F. M., and Smith, A. N.: Combined Procedure of Partial Gastrectomy and Infradiaphragmatic Vagus Resection, A. M. A. Arch. Surg. **62**:171, 1951.

evidence of a recurrent ulcer. Patients with minimal side-effects of vagotomy, such as occasional mild diarrhea, were put in this group. Several patients were also included who may have to be reclassified, since their follow-up period was for less than one year.

A patient was considered to have a vagotomy "failure" only when it was proved that he had a recurrent ulcer. Definite x-ray evidence of a crater (either duodenal or gastric or marginal), an active ulcer at reoperation, or definite ulcer symptoms associated with evidence of bleeding, including a drop in hemoglobin, were accepted as proof of a recurrent ulcer.

All of the remaining cases that did not qualify for either of the above groups were classified as "improved." The group was subdivided into *a* and *b*. Patients whose results were not considered good because of annoying side-reactions were listed under *a*. In this subgroup were included 10 patients who required subsequent operations for gastric drainage. Patients with a recurrence of ulcer symptoms

TABLE 3.—*Summary of Results* *

	Vagotomy†				Vagotomy and Gastroenterostomy†			
		Improved				Improved		
Type of Ulcer	G	a	b	F	G	a	b	F
Duodenal ulcer	11	10	9	15	24	4	3	1
Intractable	5	4	4	7	4	..	..	..
Hemorrhage	5	2	3	5	2	2	1	..
Obstruction	1	1	..	..	13	1	1	..
Perforation	..	1	1	2	1	1	1	1
Combination	..	2	1	1	4	..	..	..
Gastric ulcer	2	..	1	3	..	..	1	1
Marginal ulcer	9	..	..	3	..	..	..	..
Following gastroenterostomy	5	..	..	2	..	..	..	..
Following gastric resection	4	..	..	1	..	..	..	..
Totals	22	10	10	21	24	4	4	2

* The one case of vagotomy and gastric resection had a good result. Two cases of duodenal ulcer were lost to follow-up.

† The following abbreviations are used: G, good; a, improved with annoying side-effects; b, improved with ulcer symptoms; F, failure.

requiring a return to diet and medication were listed under *b*. In this subgroup were included a number of patients whose results will probably be considered failures ultimately, judging from the nature and severity of their symptoms.

There were two patients that were completely lost to follow-up who have been listed separately (Table 3).

There were two deaths in the series, and these results were classified as failures. One of these patients died on the first postoperative day, and the death was attributed to the operation. Postmortem examination revealed a massive atelectasis as the cause of death. The second death occurred in a young man who was admitted to the hospital with acute hemorrhage from a duodenal ulcer. The patient was vagotomized approximately one month after the cessation of bleeding. He died three months postoperatively without having been discharged from the hospital. At postmortem examination a diagnosis of periarteritis nodosum was made. Examination of the stomach revealed the presence of an active gastric ulcer, which did not appear to be associated with the periarteritis.

There were two additional deaths in the period of follow-up. One patient was operated upon 18 months after vagotomy for cancer of the rectum. He died of metastases two and one-half years later, without evidence of recurrence of his ulcer. The other patient required a gastroenterostomy 18 months after transthoracic vagotomy because of persistent gastric retention. After anterior gastroenterostomy, an ileus developed, which failed to respond to any form of therapy. The patient died several weeks after operation, and permission for postmortem examination was not obtained.

SIDE-EFFECTS OF VAGOTOMY

The undesirable side-effects observed after vagotomy were similar to those reported by previous authors (Grimson,[3] Weinberg,[6] and others). In general they were mild and transitory, with the exception of retention in patients who had not had some sort of a supplementary gastric drainage procedure.

Cardiospasm was seen in mild degree in nine patients and severely in one man who required repeated esophageal dilations over a period of a year. When seen at the five-year follow-up, he was still having episodes of difficulty in swallowing. The side-effects of transthoracic vagotomy accounted for the difficulties in all but two of these cases. Symptoms came on as soon as the patients were allowed solid food and usually were gone before the 12-month follow-up.

Diarrhea occurred in mild degree in 33 patients, somewhat less often with vagotomy alone than with vagotomy and gastroenterostomy. In general, it would occur in episodes lasting for several days at a time and would come on at varying intervals, though some patients continued to have three or four watery movements daily. Unlike the cardiospasm, it was most usually persistent over the entire period of the follow-up.

Gastric retention was seen in mild degree in 30 patients and in severe degree in 19. Side-effects of vagotomy alone were responsible for mild obstruction in all but nine of the patients and for the severe obstruction in all but two. Ten patients with severe retention required subsequent drainage operations, exclusive of patients with proved recurrent ulcers. It was impossible to predict which patients were likely to be troubled with retention postoperatively by inspecting the ulcer at the time of surgery. Over half the patients treated with vagotomy alone subdiaphragmatically had subsequent retention, while this was true in only one-third of the cases in which the procedure was done through the chest. The retention seen following vagotomy and gastroenterostomy was chiefly due to difficulty in placing the gastroenterostomy at the most dependent portion of the stomach.

A hypoglycemic syndrome, characterized by nervousness, weakness, and sweating, coming on one to two hours after meals, was seen in 15 patients. It was seen somewhat more commonly with vagotomy alone than with vagotomy and gastroenterostomy. Several of these patients were studied recently with glucose tolerance tests and showed curves which fell within a few hours to definite hypoglycemic levels, one blood sugar of 14 mg. per 100 cc. being recorded. Hypoglycemic symptoms were relieved by eating, and the patients improved with frequent small feedings.

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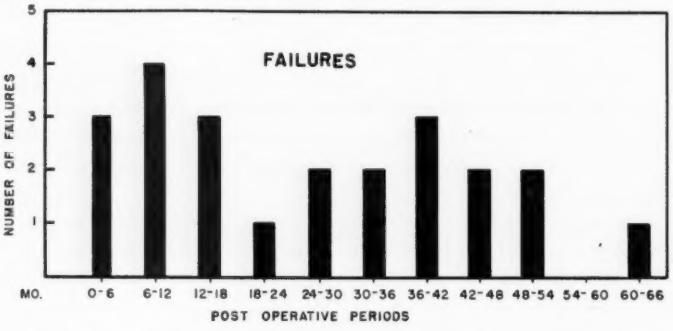
6. Weinberg, J.; Kraus, A. R.; Stempien, S. J., and Wilkins, F. B.: Vagotomy in the Treatment of Duodenal Ulcer: Results in 350 Consecutive Cases, A. M. A. Arch. Surg. **62**:161, 1951.

The side-effects following vagotomy for marginal ulcers were not included with the main group, since all of these patients had had previous gastroenterostomy or gastric resection. In general, there was slightly less diarrhea, considerably less retention, and more hypoglycemic reactions resulting from vagotomy for marginal ulcer.

There were no untoward reactions in the single case of vagotomy and gastric resection.

INSULIN TEST

The insulin test was interpreted according to Hollander's [7] criteria. Excluding those patients on whom the test was not performed because of their age or on whom it was equivocal and not repeated, there were 83 patients who had significant tests. The results were similar to those reported by Walters [4] and showed a poor correlation with clinical results. Twenty-seven patients with positive insulin tests following vagotomy and 11 with positive tests following vagotomy and gastroenterostomy had good results. This was double the number of patients with positive tests for whom the result was a failure. Ten patients with negative tests following vagotomy



Number of proved recurrences for each six-month period of follow-up.

and 15 with a positive test following vagotomy and gastroenterostomy had good results. There was only one failure after vagotomy in a patient in whom the insulin test was persistently negative. This patient had an achlorhydria after being given histamine, however, and therefore should be excluded.

COMMENT

There can be no doubt, as pointed out by Crile,[2] that the success of an operation such as vagotomy depends to a considerable extent upon the skill and experience of the surgeon. In the majority of the present group of cases the operations were performed by residents under the close supervision of eight different attending surgeons. Only six patients were operated upon by residents without having the adequacy of the vagotomy checked by a senior surgeon. Of these cases, 59 were supervised by one man, while three surgeons accounted for 82% of the operations

7. Hollander, F.: Laboratory Procedures in the Study of Vagotomy (with Particular Reference to Insulin Test), Gastroenterology **11**:419, 1948.

in this series. Of the eight supervising surgeons, four had failures on their first case. On the other hand, the surgeon who supervised 59 cases had five failures in the first 30 cases and five in the second 29. It may be that the operation should be performed only by surgeons with special interest in the problem and that it is not an operation to be done by the general surgeon.

The follow-up studies on the patients in this series were obtained, for the most part, by readmission to the hospital in either the medical or the surgical wards. For some patients, both hospital and questionnaire follow-up were available for comparison. It was interesting to discover that patients might be rather well satisfied with the operation in spite of ulcer symptoms requiring a return to their diet. One patient was essentially asymptomatic and felt that his operation was a complete success in spite of definite x-ray evidence of an ulcer crater on repeat gastrointestinal series.

It might be expected that the largest number of failures would occur within the first two years of follow-up. Actually, by graphing the number of proved recurrences for each six-month period of follow-up, a bar graph was obtained (Chart) that had two peak rates, one at 12 months and the other at 42 months. There were more recurrences after 24 months than before, and the rate of recurrence was fairly consistent up to the 60-month follow-up.

While it is obviously unwise to draw many conclusions from the foregoing material, several things are apparent. The use of vagotomy alone, whether performed above or below the diaphragm, was associated with the greatest incidence of failure and annoying side-reactions. Vagotomy with gastroenterostomy gave much better results in the treatment of duodenal ulcer, but there was one proved failure and three patients with ulcer symptoms among the 33 subjected to this procedure. There was also one case classified as one of vagotomy alone in which a marginal ulcer perforated one year after a gastroenterostomy necessitated by severe retention following vagotomy. There were likewise two more perforated marginal ulcers within three months of operation occurring in the next 30 cases following the present series. The results of vagotomy in the treatment of gastric ulcer were poor, and the risk of cancer was illustrated.

At present, we feel that vagotomy with gastroenterostomy should be reserved for the older poor-risk patients when resection seems unduly hazardous. It may likewise have some place in the treatment of poor-risk patients with marginal ulcers.

SUMMARY

One hundred patients treated by vagotomy for complicated peptic ulcers were followed up to five or more years, with a hospital follow-up of 96%.

Vagotomy alone was performed 46 times for duodenal ulcer, 6 times for gastric ulcer, and 12 times for marginal ulcer. Vagotomy and gastroenterostomy was utilized for 33 duodenal ulcers and 2 gastric ulcers.

Vagotomy alone, whether performed above or below the diaphragm, was associated with the greatest incidence of failure and annoying side-reactions. There were 20 cases of proved recurrent ulcers in the 64 patients so treated.

Vagotomy and gastroenterostomy gave better results in the treatment of duodenal ulcer. There was 1 patient with recurrent and 3 others with ulcer symptoms among the group of 33.

There were two hospital deaths in the series, one an operative death on the first postoperative day from atelectasis, and the other three months postoperatively from periarteritis nodosum, giving a mortality of 2%.

The undesirable side-effects of vagotomy were mild and transitory, with the exception of retention in the patient who had not had a supplementary gastric drainage procedure. A hypoglycemic syndrome occurred in 15 patients, somewhat more frequently in those with vagotomy alone.

There was poor correlation between the Hollander insulin test and the clinical results, with respect to positive tests. There were no vagotomy failures among patients with persistently negative tests.

At present, we feel that vagotomy with gastroenterostomy should be reserved for the older poor-risk patients with duodenal or marginal ulcers when resection seems unduly hazardous.

EXPERIMENTAL STUDIES WITH INTRA-ARTERIAL TRANSFUSION

Overtransfusion in the Anemic Dog and the Hypoproteinemic Dog

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IN A PREVIOUS paper [1] the effects of an overtransfusion of whole blood into the femoral artery in a series of normal dogs were studied. It was found that an intra-arterial transfusion of whole blood equal to 7% of the body weight of the dog, if administered in 30 to 60 minutes, caused the death of 30% of the dogs.

In overtransfusion in 10 normal dogs the femoral venous pressure rose an average of 7 cm. of saline; the respiratory rate rose an average of 14 respirations per minute; the pulse rate fell an average of 60 beats per minute, and the blood pressure tended to fall.

The present study was undertaken to see how a dog with a lowered red blood cell count or lowered plasma proteins would respond to the same sized intra-arterial transfusion of whole blood.

METHODS

Mongrel dogs weighing about 10 kg. were used. The animals were isolated for several weeks, dewormed, and vaccinated against distemper. When it seemed certain that the animals were in good health, two series of dogs were prepared. Phlebotomies of 100 to 200 cc. of blood into citrate solution were carried out with aseptic precautions. In one group of dogs the plasma was reinfused. In another group the erythrocytes were reinfused. The venous hematocrits, total plasma proteins, serum albumin, and serum globulin levels were measured at intervals.

In the anemic series, an effort was made to lower the hematocrit level to 20 or less while maintaining the serum total protein at 7.0 gm. per 100 cc. In the hypoproteinemic series, an effort was made to lower the serum total protein level to 5 gm. per 100 cc. or less while maintaining the hematocrit at 40.

When it was felt that the animals had been properly prepared, an intra-arterial transfusion was given the next day. The animal was lightly anesthetized with intravenous injections of

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1. Beattie, E. J., Jr.; Thistlethwaite, J. R.; Blades, B., and Wood, O.: Experimental Studies with Intra-Arterial Transfusion: Overtransfusion of Normal Dogs, Surgery **31**:411, 1952.

pentobarbital (nembutal®) anesthesia. Whole blood equal to 7% of the body weight of the recipient animal was aseptically given in 30 to 60 minutes into the femoral artery. The blood employed had been collected aseptically from donor dogs into acid citrate dextrose solution and had been kept in a refrigerator at 4 C. until used. The donor blood was usually a few days old at the time of transfusion.

During the transfusion, the femoral venous pressure was recorded with a saline manometer. The respiratory rate was counted. The pulse rate and the femoral artery blood pressure were

TABLE 1.—*Anemic Dogs*

Dog No.	Total Protein, Gm./100 Cc.	Hematocrit	Change in Venous Pressure, Gm. Saline	Change in Respiratory Rate/Min.	Change in Pulse Rate/Min.	Change in Blood Pressure, Mm. Hg	Outcome
CY 387	9.8	16	+ 2	—40	—40	—	Living and well
CY 391	5.8	12	+ 9	+ 6	—20	—	Living and well
CY 393	6.8	22	— 1	+ 9	0	—	Died, 48 hr.
CY 396	8.5	14	+12	+ 9	+ 5	....	.....
CY 390	...	22	+ 5	+ 1	—50	—	Living and well
DG 819	7.0	26	+ 6	0	—50	—50/—40	Living and well
DJ 843	6.0	24	+ 8	— 6	+10	—20	Living and well
DJ 864	6.5	22	+21	0	—25	mean —115/—80	Living and well
DN 1,039	4.4	22	+ 8	+40	....	....	Living and well
Average change			+ 8	+ 2	—20	....	Mortality rate, 10%

TABLE 2.—*Hypoproteinemic Dogs*

Dog No.	Total Protein, Gm./100 Cc.	Hematocrit	Change in Venous Pressure, Gm. Saline	Change in Respiratory Rate/Min.	Change in Pulse Rate/Min.	Change in Blood Pressure, Mm. Hg	Outcome
CO 390	4.9	42	....	+ 5	—24	....	Living and well
CO 931	4.8	42	....	+ 4	—28	....	Living and well
CO 933	5.2	32	+10	+34	—20	....	Died, 48 hr.
CO 937	4.5	40	— 3	+ 4	—15	—20/—15	Living and well
DC 667	4.5	57	+11	+14	—55	+10/+50	Living and well
DD 675	5.0	54	+ 6	+ 7	—20	+10/+20	Living and well
DF 759	5.2	38	+11	— 4	—30	—15/+ 5	Living and well
DG 445	4.2	36	+13	0	—20	—10/+ 5	Living and well
DF 766	4.2	46	+ 9	+ 4	—50	0/+ 5	Living and well
DG 813	5.0	53	+18	+35	0	0/ 0	Living and well
Average change			+ 9	+10	—25	....	Mortality rate, 10%

recorded by means of a cannula in the opposite femoral artery attached to a Sanborn electromanometer. The animals were observed for several weeks after the overtransfusion.

RESULTS

Approximately 30 animals were used to prepare the 19 animals receiving overtransfusion.

Overtransfusion was given to nine anemic animals. Results of these experiments are summarized in Table 1. The hematocrit readings ranged from 112 to 26, the average hematocrit level being 20. The total serum proteins of these animals ranged from 6.0 to 9.8 gm. per 100 cc. except for one animal in which the total protein was 4.4 gm. per 100 cc.

Eight anemic animals survived the overtransfusions uneventfully. One animal died within 48 hours after the overtransfusion, seemingly from the effects of the overtransfusion. In these animals the notable physiological changes were an average rise in the femoral venous pressure of 8 cm. of saline and an average fall in pulse rate of 20 beats per minute.

Ten hypoproteinemic animals were given overtransfusions. The results of these experiments are summarized in Table 2. The total serum proteins ranged from 4.2 to 5.2 gm. per 100 cc. The hematocrit readings ranged from 36 to 57 in nine animals. One animal had a hematocrit reading of 32.

Nine hypoproteinemic animals survived the overtransfusions uneventfully. In this series, also, one animal died within 48 hours, seemingly from the effects of the overtransfusion. The physiological changes in this series were comparable to those of the anemic group. There was an average rise in femoral venous pressure of 9 cm. of saline. There seemed to be a more noticeable rise in the respiratory rate of 10 respirations per minute. The pulse rate fell an average of 25 beats per minute. The blood pressure changes were not consistent.

SUMMARY

The anemic or the hypoproteinemic dog tolerates an intra-arterial overtransfusion of whole blood equal to 7% of body weight in 30 to 60 minutes as well as or better than the normal dog.

Of the anemic or hypoproteinemic dogs, 10% died, as compared with a 30% mortality rate in the normal dogs.

The venous pressure rise in all dogs was about the same.

The decrease in pulse rate and blood pressure was more marked in the normal dogs.

Case Reports

SURGICAL EXPERIENCE WITH CORTICOTROPIN IN ULCERATIVE COLITIS

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PREVIOUS reports of perforations of the upper gastrointestinal tract in patients undergoing therapy with corticotropin (ACTH) and cortisone have been well noted.[1] A more recent report [2] of three cases of large bowel perforation occurring in ulcerative colitis patients under treatment with corticotropin is interesting.

In regard to this last report, we feel the following case presentation is warranted from a surgeon's operative point of view.

REPORT OF A CASE

A 42-year-old drug salesman was admitted to the hospital Nov. 5, 1951, complaining of marked diarrhea. His symptoms dated back to 1935, and in 1946 a definite diagnosis of chronic ulcerative colitis had been made. Since that time the free periods between his recurrent episodes of diarrhea had gradually grown shorter. These attacks were severer, with an increase in pain and in the passage of blood and mucus. He had lost 15 lb. (6.8 kg.) in the four months just prior to being hospitalized. On admission he was exceptionally uncomfortable, passing 20 to 25 stools a day.

Physical Examination.—Examination revealed a chronically ill white man in early middle age. The temperature was 100 F., pulse rate 86, and blood pressure 126/70 mm. Hg. Examination of the head, ears, nose and throat revealed nothing abnormal. Response to auscultation and percussion of the heart and lungs was within normal limits. The abdomen was flat, but voluntary guarding was present in all quadrants, and the lower half of the abdomen, especially, was tender to deep palpation. A digital rectal examination was negative. The extremities and reflexes were all within normal limits.

Laboratory Data.—On admission, the erythrocyte count was 3,400,000, with a hemoglobin level of 8 gm. per 100 cc. and a hematocrit value of 31%. The white blood count was 8,600, with no shift to the left or right. Blood chemistry studies of urea nitrogen, and total proteins with albumin-globulin ratio were all within normal limits. The reaction to the Kahn test was negative.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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1. Sloan, S.; Briggs, J. D., and Halsted, J. A.: ACTH Therapy for Ulcerative Colitis Complicated by Perforation of Coexisting Peptic Ulcer, Gastroenterology **18**:438 (July) 1951. Beck, J. C., and others: Occurrence of Peritonitis During ACTH Administration, Canad. M. A. J. **62**:423 (May) 1950.

2. Tulin, M.; Kern, F., and Almy, T. P.: Perforation of Bowel During Treatment of Ulcerative Colitis with Corticotropin: Report of 3 Cases, J. A. M. A. **150**:559 (Oct. 11) 1952.

Repeated stool examinations were negative for parasites or ova. The urinalysis showed nothing abnormal. A barium enema pictured the entire colon as tube-like in configuration, shortened, narrowed, and showing pseudopolyp formation.

Hospital Course.—Immediately after admission, sigmoidoscopy revealed a red, friable, patchy mucosa covered with exudate. The patient was placed on a regimen of bed rest, a bland diet, and phthalylsulfathiazole and methantheline bromide (banthine®). After three weeks of this therapy, the number of stools diminished to between 8 and 10 daily. However, repeat sigmoidoscopy showed no improvement in the appearance of the rectosigmoid mucosa. Treatment was then changed to camphorated tincture of opium and 3 gm. of aureomycin daily. This change in therapy did not improve his condition, and it was discontinued. In the ninth hospital week, the patient was given *p*-nitrosulfathiazole (nisulfazole®) rectal irrigations. After 20 days he still had 12 to 15 mucoid bloody stools daily, and he was considered a candidate for surgery.

On March 17, 1952, the medical staff, in conjunction with the ACTH board, recommended a total colectomy. Surgery was to follow a preoperative course of corticotropin, which was to be given intravenously according to the following schedule: 20 mg. in 1,000 cc. of 5% glucose in distilled water, over a 20-hour period in the first 24 hours; 20 mg. daily for the next four days over 12-hour periods; 20 mg. on the sixth and seventh days for 8 hours; and 20 mg. on the eighth and ninth days for 6 hours.

Twelve days after the corticotropin therapy was discontinued an ileostomy and partial colectomy to the midsigmoid was performed. At operation, the entire length of large colon seemed to be covered with an excessive amount of indurated fatty tissue. There was no evidence of any acute process. The serosa of the cecum and ascending colon could be visualized and had a slightly pinkish, granular, salt-and-pepper appearance.

The operation proceeded in the usual manner until the transverse colon was being separated from the gastrocolic omentum. At this point multiple perforations of the colon occurred during normal handling. The splenic flexure, which was not markedly bound down, separated completely from the remainder of the colon and had to be removed independently. After the colon had been removed, the distal limb was pulled through a stab wound in the left lower quadrant, and while this was being done, the remaining colon literally shredded. Because of this, an open loop for irrigation purposes could not be left outside the abdominal wall and, of necessity, was buried as a closed loop.

The patient ultimately had an uneventful postoperative course and recently underwent the remaining abdominoperineal portion of his total colectomy without incident.

COMMENT

In our hands, the planned staged colectomy for chronic ulcerative colitis has not been exceptionally difficult from a technical standpoint. Nor have we been impressed with any marked decrease in the tensile strength of the colon in such cases, except possibly in those in which the condition is acute and fulminating. The case reported was the only one in a series in which the colon literally fell apart on handling, and the only one in which extensive preoperative preparation with corticotropin was used.

Although our experience was admittedly a singular one, it was so impressive that we feel justified in adding it to other clinical observations dealing with the relationship of corticotropin and friability of the gastrointestinal tract.

LEIOMYOSARCOMA OF RECTUM

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OCCASIONALLY on digital examination of the rectum one finds a submucosal nodule. Jackman and Buie [1] have emphasized the importance of this and recommend biopsy to prove the type of lesion. Recently, we encountered a submucosal tumor of the rectum which proved to be a leiomyosarcoma. Because of the extreme rarity of such tumors, the following case report is deemed worthy.

REPORT OF A CASE

The patient was a 45-year-old woman who consulted us because of a recurrence of a smooth-muscle tumor of the rectum. Two years previously she was seen by her physician, complaining of rectal bleeding and pain following defecation. Examination disclosed a submucosal tumor on the anterior rectal wall, without ulceration of the mucosa. Through the anal canal, local excision was carried out, Jan. 23, 1950.

The mass recurred, however, and was again excised, in September, 1951. When we saw the patient in May, 1952, there was obvious recurrence confined to the submucosa. Upon reviewing the original slides, it was the opinion of the pathologist that we were dealing with a Grade 1 leiomyosarcoma of the rectum.

Except for a rather severe hypertension, she had always been in good health and had undergone no other surgical operations than those mentioned. She had suffered the usual childhood diseases and had recovered fully.

The examination disclosed a healthy-appearing, moderately obese, white woman about 45 years of age. The reaction of the eyes to light and in accommodation was normal. The teeth were in good state of repair, and the thyroid gland was not enlarged. There were no palpable lymph nodes in the neck. The breasts were free of masses. The heart beat was regular, and there were no murmurs. The lungs were clear to percussion and to auscultation. The liver was not palpably enlarged, and there were no areas of tenderness and no masses in the abdomen. A bimanual examination disclosed no abnormalities of the uterus, cervix, or adnexa, but there was a firm submucosal tumor 3 cm. in diameter growing against the posterior vaginal wall from the rectum. The tumor was somewhat bosselated, nontender, and movable. The knee and ankle reflexes were active. The blood pressure was 240/140. The blood cell count was within normal limits, and the urinalysis revealed no abnormalities.

A chest x-ray study disclosed some calcified mediastinal glands, but the lung fields were clear and the heart appeared to be normal in diameter. An intravenous urogram disclosed normal configuration of both kidney pelves and calyces, with good concentration of the dye.

On June 2, 1952, a combined abdominoperineal resection was carried out, and a sigmoid colostomy was established in the left lower quadrant of the abdomen. During the procedure it was necessary to administer 2 pt. (950 cc.) of blood, but the patient withstood the operation well.

1. Jackman, R. J., and Buie, L. A.: Submucosal Nodules of the Rectum, S. Clin. North America **24**:903-909, 1944.

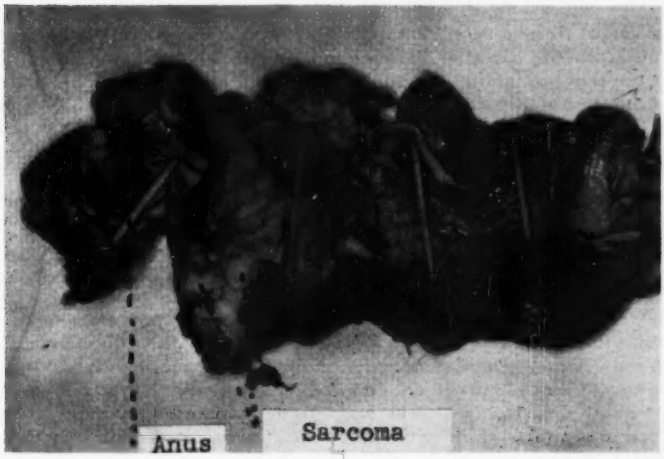

Fig. 1.—Gross specimen of rectum and anus, showing submucosal location of leiomyosarcoma.

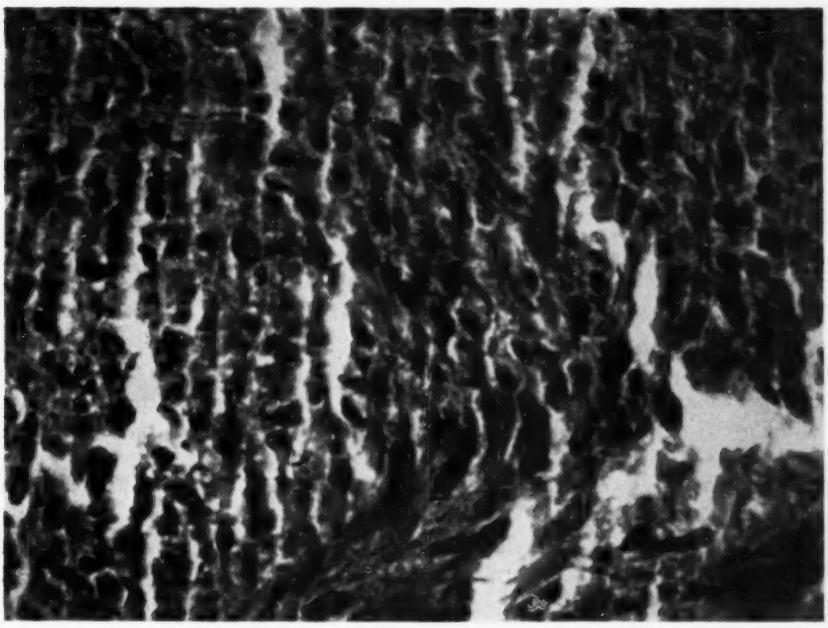

Fig. 2.—Photomicrograph of actively growing section of tumor.

The postoperative convalescence was uneventful, and she left the hospital in 17 days. Four weeks later it was necessary to rehospitalize her for drainage of a presacral pelvic abscess. She has since recovered fully and has no complaints at this time.

The pathologist reported the specimen (Fig. 1) to consist of a segment of bowel comprising the rectum and anus and measuring 20 cm. in length and 4 to 6 cm. in diameter. The external surface of the anus was grossly normal. At a distance of 3 cm. above the mucocutaneous junction, the mucosa of the rectum was roughened, and in the submucosal fat and fibrous tissue a group of five, circumscribed, white, firm nodules were present, which varied from 12 to 20 mm. in diameter. These nodules projected into the base of the mucosa but did not appear to have extended through the mucosa. They formed a mass 3 cm. in diameter in the adventitia of the rectum and anus. The upper portion of the rectum with the adventitial fat and fibrous tissue was not grossly remarkable. The mucosa in all areas was essentially normal. There were a few small yellow or white soft lymph nodes in the submucosal fat. These were 6 to 12 mm. in diameter and did not appear to be involved by tumor tissue.

Sections of the rectum revealed an intact mucosa with a very large submucosal lymphocytic infiltration. Several sections of the perirectal tumor masses revealed them to be composed of sheets of well-differentiated smooth muscle. In the muscularis of the rectum itself there were small foci of what appeared to be actively growing smooth muscle (Fig. 2). In the tumor masses the smooth muscle was well differentiated. The nuclei were hyperchromatic, and very frequently mitoses were identified. The tumor tissue masses were circumscribed, and there did not appear to be invasion of the surrounding tissue. A single lymph node from the adventitial fat appeared normal.

The diagnosis was leiomyosarcoma of the rectum.

COMMENT

Smooth-muscle tumors may occur any place in the gastrointestinal tract. They are commonest in the stomach, but when found in the rectum they are pathological rarities. Vander Espt (1881) is given credit for the earliest report of such a rectal tumor. Since then, there have been numerous reports on leiomyomas and their malignant counterparts, leiomyosarcomas, of the rectum. On critically reviewing these past reports in the light of our present knowledge, it is evident that it has been difficult to distinguish a low-grade leiomyosarcoma from a leiomyoma.[2]

Anderson, Dockerty, and Buie [3] found only 20 such tumors in the material at the Mayo Clinic over a period of 35 years. During this time, 10 of these tumors were leiomyomas and 10 were leiomyosarcomas. They estimate that smooth-muscle tumors occur once in every 2,000 to 3,000 rectal tumors.

Clinically these lesions are not characterized by any exotic symptoms. Some are asymptomatic and are disclosed on routine examination. At other times, a change in bowel habits brings the patient to the physician. In about half the cases, ulceration of the overlying mucosa takes place with gross bleeding. In some, there is definite localized pain, and occasionally a tumor may attain a large size and block the rectal canal. One ought to consider any submucosal nodule of the rectum a clinically suspicious lesion until proved otherwise.

Local excision of a leiomyosarcoma is almost invariably followed by a local recurrence, while local excision of a leiomyoma is generally curative.

Pathologically, leiomyosarcomas of the rectum blend from Grade 1 to Grade 4 tumors. It takes the expert surgical pathologist to differentiate the benign leio-

2. Hunt, V. C.: Myoma of the Rectum: Report of 4 Cases, Ann. Surg. **74**:236-244, 1921.

3. Anderson, P. A.; Dockerty, M. B., and Buie, L. A.: Myomatous Tumors of the Rectum (Leiomyomas and Myosarcomas), Surgery **28**:642-650, 1950.

myoma from the Grade 1 leiomyosarcoma. Golden and Stout [4] feel that the relative number of mitoses is directly proportional to the inherent growth capacity of the tumor and state that if two or more mitoses per high power field are present one can feel sure the tumor is malignant. However, they have noted that some clinically malignant tumors have shown very few mitoses.

A number of authors have seen metastases to the regional lymph nodes, but this is a relatively uncommon finding in leiomyosarcoma of the rectum. The mode of spread has been predominantly venous to the liver and less often by local extension.

Attempts to treat leiomyosarcoma of the rectum by radiation therapy have been universally unsuccessful.

The most that a surgeon can do is to excise the tumor locally with wide margins and to dissect the regional lymph nodes. If a tumor occurs in the rectum, an abdominoperineal operation, or a sphincter-preserving operation, if the lesion lends itself to the latter, is the procedure of choice.[5] In some of the foreign literature, local excision is recommended for a leiomyosarcoma, but this generally has not been satisfactory. All too often the tumor has spread beyond the confines amenable to the most radical surgery, and it has been the sad experience of most people that these tumors are generally not curable. Anderson, Dockerty, and Buie found that 9 of the 10 patients in their series with leiomyosarcoma were dead at the time of their report.[3]

SUMMARY

A case of leiomyosarcoma of the rectum is presented.

A discussion of the historical background, the clinical symptoms, the pathological findings, and the surgical treatment is given.

4. Golden, T., and Stout, A. P.: Smooth Muscle Tumors of the Gastrointestinal Tract and Retroperitoneal Tissues, Surg., Gynec. & Obst. **73**:784-810, 1941.

5. Goldman, M. L., and Marbury, W. B.: Sarcoma of the Rectum, Am J. Surg. **71**:387-391, 1946.

FIBROMYOMA OF THE DUODENUM

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NEW YORK

THE PURPOSE of this paper is to review the incidence and the clinical features of fibromyoma of the duodenum and to present a case report as an example of this tumor lest it be forgotten in the differential diagnosis of gastrointestinal bleeding. Such a tumor may be responsible for serious symptoms, but it may be overlooked; yet, as a rule, it is easily removed. In the literature these lesions are recorded as myomas, fibromas, leiomyomas, fibromyomas, etc. For the sake of clarity and because all these lesions contain both smooth muscle and fibrous tissue in varying amounts, the term fibromyoma is offered here to designate any of the aforementioned pathological entities.

INCIDENCE

The incidence of benign duodenal tumors found in the pavilion service of the New York Hospital from 1932 to 1951 is illustrated in the accompanying Table, with comparative figures reported by 17 other authors.[1] It will be seen that of the total 90 cases, adenomas were by far the commonest lesions, comprising 42.2%. Fibromyomas are second in frequency, with an incidence of 18.8%. Figures for the

From the Department of Surgery, the New York Hospital—Cornell Medical Center.

1. (*a*) Balfour, D. C., and Henderson, E. F.: Benign Tumors of Duodenum, Ann. Surg. **89**:30-35, 1929. (*b*) Carman, R. D.: Hemangioma of Duodenum, Am. J. Roentgenol. **8**:481, 1921. (*c*) Camp, J. D.: Myoma of Stomach and Duodenum: Report of Case, Radiology **2**:262-264, 1924. (*d*) Clifton, H. C., and Landry, B. B.: Fibromata of Intestines: Report of Case and Review of Literature, Boston M. & S. J. **197**:8-19, 1927. (*e*) Golden, R.: Nonmalignant Tumors of Duodenum, Report of 2 Cases, Am. J. Roentgenol. **20**:405-415, 1928. (*f*) Comfort, M. W.: Submucous Lipomata of Gastro-Intestinal Tract: Report of 28 Cases, Surg., Gynec. & Obst. **52**:101-118, 1931. (*g*) Hoffman, B. P., and Grayzel, D. M.: Benign Tumors of Duodenum, Am. J. Surg. **70**:394-400, 1945. (*h*) Meisel: Adenomyom des Duodenums als Aetiologie eines Ulcus duodeni, Schweiz. med. Wchnschr. **51**:430, 1921. (*i*) Morison, J. E.: Tumors of Small Intestine, Brit. J. Surg. **29**:139-153, 1941. (*j*) Raiford, T. S.: Tumors of Small Intestine, Arch. Surg. **25**:122 and 321, 1932; Tumors of Small Intestine: Their Diagnosis with Special Reference to X-ray Appearance, Radiology **16**:253-270, 1931. (*k*) Rankin, F. W., and Newell, C. E.: Benign Tumors of Small Intestine, Surg., Gynec. & Obst. **57**:501-507, 1933. (*l*) Rankin, F. W., and Grimes, A. E.: Small Bowel Tumors with Special Reference to Melena, South. Surgeon **6**:280-287, 1937. (*m*) Vogt, M. E.: Benign Perforating Duodenal Cyst Arising from Vestigial Remains of Wolffian Body, Am. J. Obst. & Gynec. **10**:798-802, 1925. (*n*) van Tienhoven, A.: Two Rare Cases of Duodenal Tumor, Nederl. tijdschr. geneesk. **65**:2629-2641, 1921. (*o*) Waugh, O. S.: Congenital Cyst of Duodenum: Report of a Case, Surg., Gynec. & Obst. **37**:785-787, 1923. (*p*) Weishaupt, Adenomyoma duodeni, Ztschr. Geburth. u. Gynäk. **78**:506-513, 1915-1916. (*q*) Wellbrock, W. L. A.: Tumors of Duodenum, Jejunum, and Ileum, J. South Carolina M. A. **27**:300-302, 1931. (*r*) Willis, A. M., and Lasersohn, M.: Benign Tumors of Duodenum, Ann. Surg. **82**:952-955, 1925.

Benign Tumors of the Duodenum

Authors	Total Cases	Adenoma	Fibro-myoma	Pancreatic Rest	Heman-gioma	Lipoma	Cystic Tumor	Lymph-angioma	Argentaf-finoma	Gastric Rest	Adeno-myoma	Fibro-adenoma
New York Hospital	9	7	1	..	..	1	..	..	..	..	..	..
Hoffman and Grayzel [1g]	14	4	1	6	..	1	..	1	..	1	..	..
Rankin and Newell [1k]	14	5	6	..	2	..	..	1	..	..	..	..
Golden [1e]	16	12	3	..	1	..	..	..	..	..	..	..
Raiford [1j]	15	4	1	2	1	3	1	..	2	..	..	1
Balfour and Henderson [1a]	6	3	2	..	1	..	..	..	..	..	..	..
Morison [1i]	4	..	..	3	..	..	..	..	..	..	1	..
Carman [1b]	1	..	..	..	1	..	..	..	..	..	..	..
Camp [1c]	1	..	1	..	..	..	..	..	..	..	..	..
Comfort [1f]	1	..	..	..	..	1	..	..	..	..	..	..
Wellbrock [1q]	1	..	..	..	..	1	..	..	..	..	..	..
Vaccari	1	..	1	..	..	..	..	..	..	..	..	..
Weishaupt [1p]	1	1	..	..	..	..	..	..	..	..	..	..
Waugh [1o]	1	..	..	..	..	..	1	..	..	..	..	..
Willis and Lasersohn [1r]	2	2	..	..	..	..	..	..	..	..	..	..
Vogt [1m]	1	..	..	..	..	..	1	..	..	..	..	..
Meisel [1h]	1	..	..	..	..	..	..	..	..	..	1	..
Van Tienhoven [1n]	1	..	1	..	..	..	..	..	..	..	..	..
Total no.	90	38	17	11	6	7	3	2	2	1	2	1
Total %	..	42.2	18.8	12.2	6.6	7.7	3.3	2.2	2.2	1.1	2.2	1.1

other benign tumors are as follows: pancreatic rests, 12.2%; lipomas, 7.7%; hemangiomas, 6.6%; cystic tumors, 3.3%; lymphangiomas, 2.2%; argentaffinomas, 2.2%, and, finally, gastric rests, 1.1%, and fibroadenomas 1.1%. This incidence is similar to the findings by Bockus.[2] Although the frequency of malignant change has not been established, Bockus estimates that about 7% of adenomatous polyps and about 20% of fibromyomas become malignant.

CLINICAL FEATURES

X-ray findings in the duodenum are not as valuable in diagnosis as they are in other locations; however, the careful and intelligent correlation of clinical findings with x-ray examination may strongly suggest the diagnosis preoperatively. The importance of this correlation deserves emphasis because there is no characteristic clinical picture. Raiford has enumerated the following clinical features, which, when present, may be found in any combination.

Symptoms.—1. Pain: Pain is usually felt in the epigastrium. In some cases it is localized in the right upper quadrant, thus simulating gall-bladder disease. It may or may not be preceded by fullness and discomfort, depending on the degree of obstruction. If mucosa is eroded the picture of duodenal ulcer may be simulated with a pattern of pain—food—relief—pain two or three hours after eating. In cases of chronic obstruction, attacks may remit completely only to be followed by an exacerbation of pain.

2. Nausea and Vomiting: The symptoms precede the onset of pain from two to five weeks and parallel the degree of obstruction. With complete occlusion there is copious watery regurgitation containing particles of undigested food—bile stained if the obstruction is below the ampulla of Vater. Dehydration, toxemia, alkalosis and prostration are all secondary symptoms depending upon the extent and degree of vomiting.

3. Distention: The complaint is frequent in the presence of duodenal obstruction. At first there may be only a sensation of fullness but this later becomes oppressive and interferes with respiration, giving a sensation of a constricting band around the lower chest.

4. Diarrhea: Diarrhea is usually present but not marked and may alternate with constipation.

5. Hematemesis and/or Melena: Hematemesis may be so great as to endanger life from loss of blood. Bleeding may be present when the tumor has ulcerated or, according to Goldschmidt, in myomas which have a definite tendency to bleed.

Physical Signs.—1. Tenderness: Tenderness is diffuse as a rule, but may be more intense in the right upper quadrant. It is seldom exquisite, and no rigidity can be felt.

2. Palpation: Benign tumors are usually attached loosely and are movable. If the lesion is of sufficient size, it may be palpable.

3. Distention: This is a marked feature with complete obstruction. It may be caused by a dilated stomach or a dilated duodenum.

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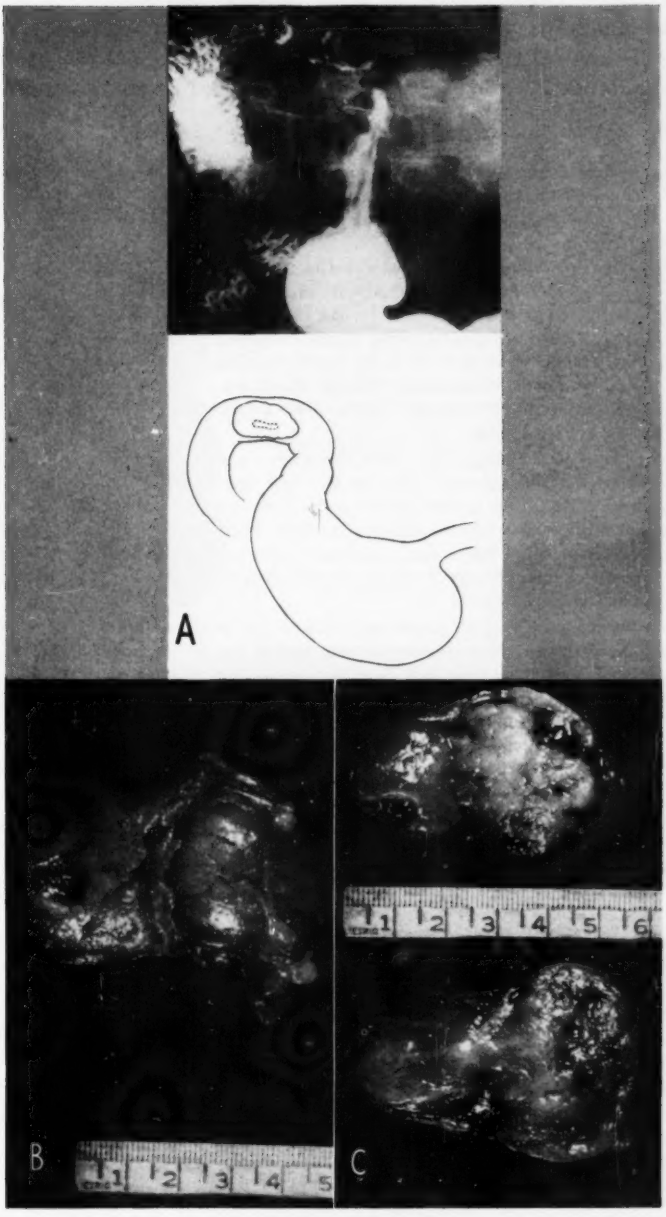
2. Bockus, H. L., and others: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1944, Vol. 2.



A, roentgenogram, with artist's impression, showing irregularity of second portion of duodenum. In center of dilated area is a small collection of barium. *B*, photograph of specimen, showing intraluminal and extraluminal portions. *C*, photograph of cut specimen.

4. Succussion Splash: This is one of the most constant signs of gastroduodenal dilatation but demands the presence of air for its occurrence.

Blood Picture.—Extremely low red cell counts are suggestive of myomas or of malignant growths. The white cell count may be affected by necrosis in the tumor.

REPORT OF A CASE

The patient entered the New York Hospital with a diagnosis of anemia of unknown origin. X-ray examination of the gastrointestinal tract revealed irregularities in the second portion of the duodenum; at exploratory laparotomy this was confirmed, and a tumor was discovered at this site.

M. S., a 54-year-old white man, was admitted to the New York Hospital in October, 1951, complaining of weakness of five weeks' duration. He had been treated for anemia outside the hospital. For four days prior to admission he had experienced dull localized epigastric discomfort, unrelated to food but relieved by taking magnesia magma. There were no other symptoms referable to the gastrointestinal tract, or to the cardiorespiratory system, to blood dyscrasias, or to acute infectious disease. On admission the only significant findings were tenderness to deep palpation in the epigastrium, hemoglobin content of 8.5 gm. per 100 cc., red blood cell count of 3,500,000, and a 2+ guaiac stool.

Because of the clinical findings, the patient was given a regimen for bleeding ulcer, and 1,250 cc. of whole blood was administered during the next few days. The gastrointestinal x-ray series indicated an irregularity of the second portion of the duodenum, consisting mainly of narrowing of the proximal segment with marked dilation beyond it. The mucosal pattern appeared normal; however, in the center there was a small persistent collection of barium. This was interpreted as an extramucosal lesion with ulceration or diverticulum formation, and a diagnosis of carcinoma of the duodenum was made.

Operation.—On exposure of the duodenum a bulbous red firm tumor mass was found on the anterior surface of the second portion of the intestine at the site indicated by the x-rays. It measured approximately 6 by 4 cm. and on palpation was felt to extend into the lumen of the duodenum; the intraluminal and extraluminal portions seemed to be equal in size. The tumor was freely movable; there were no enlarged regional lymph nodes. Several large vessels entered the lesion from the medial edge where it bordered on the pancreas. An elliptical incision was made in the duodenum over the tumor, which was excised completely; the incision in the intestine was closed transversely. Because of the questionable nature of the lesion, frozen sections were made, and these showed fibromyoma.

Pathologic Examination (by Dr. John M. Pierce).—The specimen consists of an irregularly ovoid encapsulated mass 6 cm. in length and 3.6 cm. in width. Its external surface is covered by a smooth light-tan capsule 2 mm. in thickness, which is firmly adherent to the underlying mass of tissue. A small ulceration is present on the mucosal side of the specimen.

Microscopic Examination.—This reveals anastomosing bands of smooth muscle and fibrous tissue. Some areas are edematous and contain loosely arranged fibers between which are infiltrating lymphocytes and plasma cells. Many dilated endothelium-lined spaces course through the tumor. The muscle and fibrous tissue cells are elongated, with large oval nuclei and abundant acidophilic cytoplasm. There is no evidence of malignant change. The mucosa over the tumor is intact save for one small area of superficial ulceration.

Diagnosis.—The diagnosis was fibromyoma of the duodenum.

Course.—The postoperative course was uncomplicated, and the patient was discharged from the hospital on the ninth postoperative day.

SUMMARY

The incidence and clinical features of fibromyoma of the duodenum are presented. The incidence is compared with that of other benign tumors occurring in this location.

A case of fibromyoma of the duodenum is reported.

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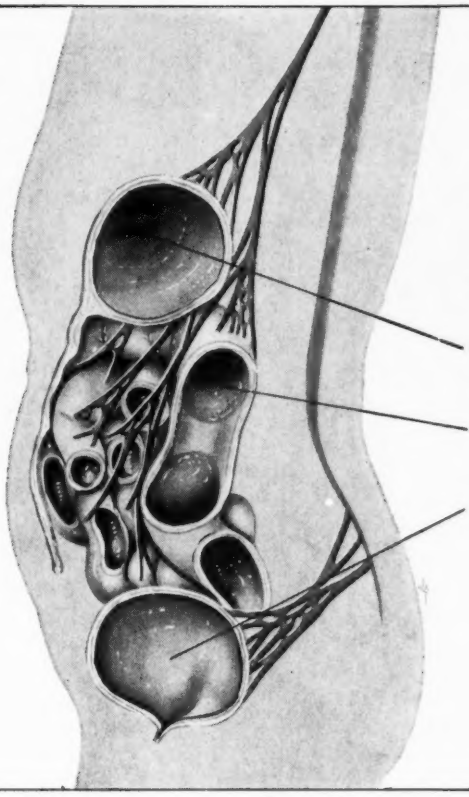

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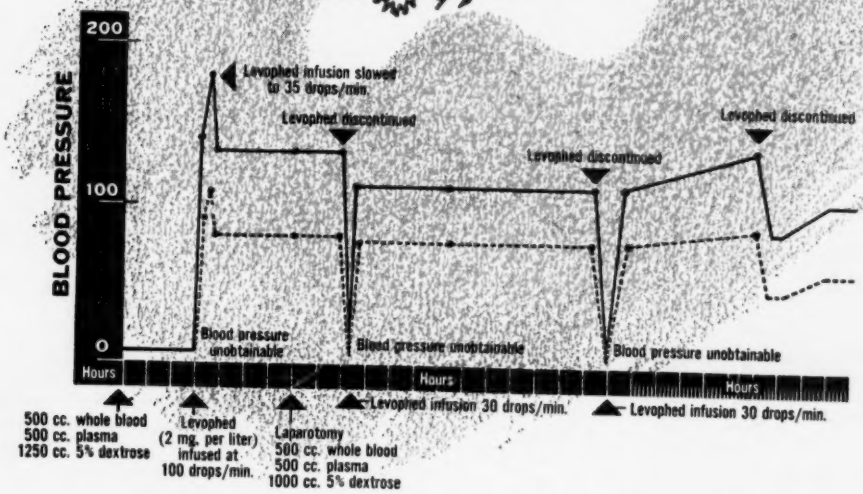

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